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Boehringer Ingelheim Pharma GmbH & Co. KG

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., BOEHRINGER INGELHEIM INTERNATIONAL GMBH, and BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, Plaintiffs, v. SANDOZ INC., Defendant.	**Civil Action No. _____** **(Filed Electronically)**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, and Boehringer Ingelheim Pharma GmbH & Co. KG (collectively, "Plaintiffs" or "Boehringer Ingelheim") by their undersigned attorneys, bring this action against Sandoz, Inc. ("Sandoz"), and hereby allege as follows:

NATURE OF THE ACTION

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. § 1, *et seq*., and in particular under 35 U.S.C §§ 271 (a–c, e–g), arises

from Sandoz's submission of Abbreviated New Drug Application ("ANDA") No. 210703 to the United States Food and Drug Administration ("FDA"). Through this ANDA, Sandoz seeks approval to market a generic version of the pharmaceutical product GILOTRIF® (afatinib) tablets prior to the expiration of United States Patent Nos. RE 43,431; 8,426,586; and 9,539,258 (collectively, the "patents-in-suit"). Plaintiffs seek injunctive relief precluding infringement, attorneys' fees, and any other relief the Court deems just and proper.

2. This is also an action under 28 U.S.C. §§ 2201–02 for a declaratory judgment of patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, *et seq*., and in particular under 35 U.S.C. §§ 271(a–c, e–g).

THE PARTIES

3. Plaintiff Boehringer Ingelheim Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Plaintiff Boehringer Ingelheim International GmbH is a private limited liability company organized and existing under the laws of Germany, having a principal place of business at Binger Strasse 173, 55216 Ingelheim, Germany.

5. Plaintiff Boehringer Ingelheim Pharma GmbH & Co. KG is a corporation organized and existing under the laws of Germany, having a principal place of business at Binger Str. 173, Ingelheim Am, Rhein Rheinland-Pfalz 55218, Germany.

6. On information and belief, Sandoz, Inc. is a corporation organized and existing under the laws of the State of Colorado, having its principal place of business at 100 College Road West, Princeton, New Jersey 08540. On information and belief, Sandoz is in the business

of marketing, distributing, and selling, in the State of New Jersey and throughout the United States, pharmaceutical drugs, including generic pharmaceutical drugs manufactured by Sandoz.

7. On information and belief, Sandoz prepared and submitted ANDA No. 210703 (the "Sandoz ANDA") and continues to collaborate in seeking FDA approval of that application.

8. On information and belief, Sandoz intends to commercially manufacture, market, offer for sale, and sell the product described in the Sandoz ANDA (the "ANDA Product") throughout the United States, including in the State of New Jersey, in the event the FDA approves the Sandoz ANDA.

JURISDICTION AND VENUE

9. This civil action for patent infringement arises under the patent laws of the United States, including 35 U.S.C. § 271, and alleges infringement of United States Patent Nos. RE 43,431 ("the '431 patent"); 8,426,586 ("the '586 patent"); and 9,539,258 ("the '258 patent"). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

10. On information and belief, this Court has personal jurisdiction over Sandoz because Sandoz, Inc. is a corporation with a principal place of business in New Jersey.

11. This Court also has personal jurisdiction over Sandoz because it has continuous and systematic contacts with New Jersey. Further, Sandoz has committed, or aided, abetted, contributed to and/or participated in the commission of, acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufactures GILOTRIF® for sale and use throughout the United States, including this Judicial District.

12. Venue is proper in this District pursuant to 28 U.S.C. § 1400. Venue is proper because on information and belief, Sandoz has a regular and established principal place of business in New Jersey.

BOEHRINGER INGELHEIM'S APPROVED GILOTRIF® DRUG PRODUCT AND PATENT

13. Boehringer Ingelheim makes and sells GILOTRIF®, a product used in the first-line treatment of metastatic non-small cell lung cancer ("NSCLC") where the tumors have epidermal growth factor receptor ("EGFR") exon 19 deletions or exon 21 (L858R substitution mutations). GILOTRIF® is also used to treat metastatic, squamous NSCLC that progresses after platinum-based chemotherapy. The active ingredient in GILOTRIF® is afatinib. A true and correct copy of the prescribing label for GILOTRIF® is attached as Exhibit D.

14. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application ("NDA") No. 201292 for GILOTRIF® and the licensee of the patents-in-suit. The FDA approved NDA No. 201292 for GILOTRIF® in July 2013, and granted GILOTRIF® five years of regulatory exclusivity for a new chemical entity pursuant to 21 C.F.R. § 314.108, which expires on July 12, 2018. The FDA also granted GILOTRIF® orphan drug exclusivity pursuant to 21 C.F.R. § 316.31.

15. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '431 patent, which is listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the "Orange Book") for GILOTRIF®. Boehringer Ingelheim International GmbH owns the '586 patent and the '258 patent, which are also listed in the "Orange Book" for GILOTRIF®.

16. The '431 patent, entitled, "Quinazoline Derivatives and Pharmaceutical Compositions Containing Them," is a reissue of United States Patent No. 7,019,012. The '431

patent was duly and lawfully issued by the United States Patent and Trademark Office ("USPTO") on May 29, 2012. A true and correct copy of the '431 patent is attached as Exhibit A.

17. The '586 patent, entitled, "Process for Preparing Amino Crotonyl Compounds," was duly and lawfully issued by the USPTO on April 23, 2013. A true and correct copy of the '586 patent is attached as Exhibit B.

18. The '258 patent, entitled, "Quinazoline Derivatives for the Treatment of Cancer Diseases," was duly and lawfully issued by the USPTO on January 10, 2017. A true and correct copy of the '258 patent is attached as Exhibit C.

SANDOZ'S ANDA

19. On information and belief, Sandoz has submitted or caused to be submitted ANDA No. 210703 to the FDA under 21 U.S.C. § 355(j), in order to obtain approval to engage in the commercial manufacture, use, or sale of afatinib dimaleate tablets, as a purported generic version of GILOTRIF®, prior to the expiration of the patents-in-suit.

20. On information and belief, on or about September 7, 2017, Sandoz mailed Plaintiffs a letter regarding "AFATINIB DIMALEATE (GILOTRIF®) TABLET EQ. 20MG BASE, EQ. 30MG BASE, AND EQ. 40MG BASE: Notification of Certification of Invalidity, Unenforceability and/or Non-infringement for U.S. Patent Nos. RE 43,431, 8,426,586, 9,539,258, and 8,545,884 Pursuant to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355G)(2)(B)(iv) and 21 C.F.R. § 314.95)" (the "Notice Letter"). The Notice Letter represented that Sandoz had submitted to the FDA ANDA No. 210703 and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Sandoz ANDA before the expiration of the patents listed in the Orange

Book for GILOTRIF®. Hence, Sandoz's purpose in submitting the Sandoz ANDA is to manufacture and market the ANDA Product before the expiration of the patents-in-suit.

21. Sandoz's Notice Letter stated that the Paragraph IV certification in the Sandoz ANDA alleges that the '431 patent, the '586 patent, and the '258 patent are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

22. Sandoz's Notice Letter contained a purported detailed statement of the factual and legal basis for its opinion that the '431 patent, the '586 patent, and the '258 patent are invalid, unenforceable, or not infringed by the manufacture, use, or sale of the ANDA Product ("Detailed Statement").

23. On information and belief, Sandoz has participated in the preparation and submission of the Sandoz ANDA, has provided material support to the preparation and submission of the Sandoz ANDA, and intends to support the further prosecution of the Sandoz ANDA.

24. On information and belief, if the FDA approves the Sandoz ANDA, Sandoz will manufacture, offer for sale, or sell the ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

25. Alternatively, on information and belief, if the FDA approves the Sandoz ANDA, Sandoz will actively induce or contribute to the manufacture, use, offer for sale, or sale of the ANDA Product.

26. This action is being brought pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) within forty-five days of Plaintiffs' receipt of the Notice Letter.

COUNT I
INFRINGEMENT OF THE '431 PATENT

27. Plaintiffs incorporate by reference paragraphs 1–26 as if fully set forth herein.

28. On information and belief, Sandoz has submitted or caused the submission of the Sandoz ANDA to the FDA, and continues to seek FDA approval of the Sandoz ANDA.

29. Sandoz has infringed the '431 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Sandoz ANDA with a Paragraph IV certification and seeking FDA approval of the Sandoz ANDA prior to the expiration of the '431 patent.

30. On information and belief, if the Sandoz ANDA is approved, Sandoz and its affiliates will make, sell, offer for sale, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '431 patent.

31. Sandoz's commercial manufacture, use, sale, offer for sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '431 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 210703, Sandoz will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '431 patent.

32. Sandoz had actual and constructive notice of the '431 patent prior to filing the Sandoz ANDA, and was aware that the filing of the Sandoz ANDA with the request for FDA approval prior to the expiration of the '431 patent would constitute an act of infringement of the '431 patent. Sandoz had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the '431 patent.

33. Sandoz's Detailed Statement in the Notice Letter lacks any sufficient contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the '431 patent.

34. In addition, Sandoz filed the Sandoz ANDA without adequate justification for asserting the '431 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Sandoz's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '431 patent renders this case "exceptional" under 35 U.S.C. § 285.

35. Plaintiffs will be irreparably harmed if Sandoz is not enjoined from infringing, and from actively inducing or contributing to the infringement of the '431 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Sandoz, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '431 PATENT

36. Plaintiffs incorporate by reference paragraphs 1–35 as if fully set forth herein.

37. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

38. On information and belief, if the Sandoz ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Sandoz and its affiliates.

39. On information and belief, Sandoz knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Sandoz ANDA and Sandoz will therefore contribute to the infringement of and/or induce the

infringement of one or more claims of the '431 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

40. On information and belief, Sandoz's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Sandoz ANDA. Any such conduct before the '431 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '431 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

41. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Sandoz concerning liability for the infringement of the '431 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

42. Plaintiffs will be substantially and irreparably harmed by Sandoz's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

43. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT III
INFRINGEMENT OF THE '586 PATENT

44. Plaintiffs incorporate by reference paragraphs 1–43 as if fully set forth herein.

45. On information and belief, Sandoz has submitted or caused the submission of the Sandoz ANDA to the FDA, and continues to seek FDA approval of the Sandoz ANDA.

46. Sandoz has infringed the '586 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Sandoz ANDA with a Paragraph IV certification and seeking FDA approval of the Sandoz ANDA prior to the expiration of the '586 patent.

47. On information and belief, if the Sandoz ANDA is approved, Sandoz and its affiliates will make, sell, offer for sale, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '586 patent.

48. Sandoz's commercial manufacture, use, sale, offer for sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '586 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 210703, Sandoz will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '586 patent.

49. Sandoz had actual and constructive notice of the '586 patent prior to filing the Sandoz ANDA, and was aware that the filing of the Sandoz ANDA with the request for FDA approval prior to the expiration of the '586 patent would constitute an act of infringement of the '586 patent. Sandoz had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the '586 patent.

50. Sandoz's Detailed Statement in the Notice Letter lacks any sufficient contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the '586 patent.

51. In addition, Sandoz filed the Sandoz ANDA without adequate justification for asserting the '586 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Sandoz's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '586 patent renders this case "exceptional" under 35 U.S.C. § 285.

52. Plaintiffs will be irreparably harmed if Sandoz is not enjoined from infringing, and from actively inducing or contributing to the infringement of the '586 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Sandoz, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT IV
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '586 PATENT

53. Plaintiffs incorporate by reference paragraphs 1–52 as if fully set forth herein.

54. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

55. On information and belief, if the Sandoz ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Sandoz and its affiliates.

56. On information and belief, Sandoz knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Sandoz ANDA and Sandoz will therefore contribute to the infringement of and/or induce the

infringement of one or more claims of the ’586 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

57. On information and belief, Sandoz’s infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Sandoz ANDA. Any such conduct before the ’586 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the ’586 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

58. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Sandoz concerning liability for the infringement of the ’586 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

59. Plaintiffs will be substantially and irreparably harmed by Sandoz’s infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

60. This case is exceptional, and Plaintiffs are entitled to an award of attorneys’ fees under 35 U.S.C. § 285.

COUNT V
INFRINGEMENT OF THE ’258 PATENT

61. Plaintiffs incorporate by reference paragraphs 1–60 as if fully set forth herein.

62. On information and belief, Sandoz has submitted or caused the submission of the Sandoz ANDA to the FDA, and continues to seek FDA approval of the Sandoz ANDA.

63. Sandoz has infringed the ’258 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Sandoz ANDA with a Paragraph IV certification and seeking FDA approval of the Sandoz ANDA prior to the expiration of the ’258 patent.

64. On information and belief, if the Sandoz ANDA is approved, Sandoz and its affiliates will make, sell, offer for sale, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, directly infringing the '258 patent.

65. Sandoz's commercial manufacture, use, sale, offer for sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '258 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 210703, Sandoz will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '258 patent.

66. On information and belief, upon FDA approval of ANDA No. 210703, Sandoz will market and distribute the ANDA Product to resellers, pharmacies, hospitals and other clinics, health care professionals, and end users of the ANDA Product. On information and belief, Sandoz will also knowingly and intentionally accompany the ANDA Product with a product label and product insert that will include instructions for using and administering the ANDA Product. Accordingly, Sandoz will induce health care professionals, resellers, pharmacies, and end users of the ANDA Product to directly infringe one or more claims of the '258 patent. In addition, on information and belief, Sandoz will encourage acts of direct infringement with knowledge of the '258 patent and knowledge that it is encouraging infringement.

67. Sandoz had actual and constructive notice of the '258 patent prior to filing the Sandoz ANDA, and was aware that the filing of the Sandoz ANDA with the request for FDA approval prior to the expiration of the '258 patent would constitute an act of infringement of the '258 patent. Sandoz had no reasonable basis for asserting that the commercial manufacture, use,

offer for sale, or sale of the ANDA Product will not contribute to the infringement of and/or induce the infringement of the ’258 patent.

68. Sandoz’s Detailed Statement in the Notice Letter lacks any sufficient contention that the ANDA Product will not infringe, contribute to the infringement of, or induce the infringement of the ’258 patent.

69. In addition, Sandoz filed the Sandoz ANDA without adequate justification for asserting the ’258 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Sandoz’s conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the ’258 patent renders this case “exceptional” under 35 U.S.C. § 285.

70. Plaintiffs will be irreparably harmed if Sandoz is not enjoined from infringing, and from actively inducing or contributing to the infringement of the ’258 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Sandoz, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT VI
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’258 PATENT

71. Plaintiffs incorporate by reference paragraphs 1–70 as if fully set forth herein.

72. Plaintiffs’ claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

73. On information and belief, if the Sandoz ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Sandoz and its affiliates.

74. On information and belief, Sandoz knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Sandoz ANDA and Sandoz will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '258 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

75. On information and belief, Sandoz's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after the FDA approves the Sandoz ANDA. Any such conduct before the '258 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '258 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g).

76. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Sandoz concerning liability for the infringement of the '258 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

77. Plaintiffs will be substantially and irreparably harmed by Sandoz's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

78. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

REQUEST FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Sandoz infringes the '431 patent, the '586 patent, and the '258 patent under 35 U.S.C. § 271(e)(2)(A);

B. A declaratory judgment that under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g), Sandoz's commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of the ANDA Product, or inducing or contributing to such conduct, would constitute infringement of one or more claims of the '431 patent, the '586 patent, and the '258 patent;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Sandoz, its affiliates and subsidiaries, and all persons and entities acting in concert with Sandoz from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes the '431 patent, the '586 patent, and the '258 patent, including the ANDA Product described in ANDA No. 210703;

D. The entry of an order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of ANDA No. 210703 shall be no earlier than the expiration date of the '431 patent, the '586 patent, and the '258 patent, or any later expiration of exclusivity for the '431 patent, the '586 patent, and the '258 patent, including any extensions or regulatory exclusivities;

E. A declaration under 28 U.S.C. § 2201 that if Sandoz, its officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engages in the commercial manufacture, use, offer for sale, sale and/or importation of the product described in

ANDA No. 210703, it will constitute an act of direct and/or indirect infringement of the '431 patent, the '586 patent, and the '258 patent;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Sandoz engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes the '431 patent, the '586 patent, and the '258 patent, or induces or contributes to such conduct, prior to the expiration of the '431 patent, the '586 patent, and the '258 patent, or any later expiration of exclusivity for the '431 patent, the '586 patent, and the '258 patent, including any extensions or regulatory exclusivities;

G. The entry of judgment declaring that Sandoz's acts render this case an exceptional case, and awarding Plaintiffs their attorneys' fees pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

H. An award to Plaintiffs of their costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: October 20, 2017

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the following captioned actions are related to the matter in controversy because the matter in controversy involves United States Patent No. 8,426,586 and the same drug product:

- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Aurobindo Pharma USA Inc., et al.*, Civil Action No. 17-7887 (MAS)(LHG);
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Hetero USA Inc., et al.*, Civil Action No. 17-7923 (MAS)(LHG);
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. MSN Laboratories Private Limited, et al.*, Civil Action No. 17-8399 (MAS)(LHG); and
- *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.,* Civil Action No. 17-8819.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: October 20, 2017

By: s/ Charles M. Lizza

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EXHIBIT A

US00RE43431E

(19) **United States**

(12) **Reissued Patent**

Himmelsbach et al.

(10) **Patent Number: US RE43,431 E**

(45) **Date of Reissued Patent: May 29, 2012**

(54) **QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

(75) Inventors: **Frank Himmelsbach**, Mittelbiberach (DE); **Elke Langkopf**, Biberach an der Riss (DE); **Stefan Blech**, Warthausen (DE); **Birgit Jung**, Laupheim (DE); **Anke Baum**, Vienna (AT); **Flavio Solca**, Vienna (AT)

(73) Assignee: **Boehringer Ingelheim Pharma GmbH & Co. KG**, Ingelheim am Rhein (DE)

(21) Appl. No.: **12/542,929**

(22) Filed: **Aug. 18, 2009**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **7,019,012**
Issued: **Mar. 28, 2006**
Appl. No.: **10/023,099**
Filed: **Dec. 17, 2001**

U.S. Applications:

(60) Provisional application No. 60/259,201, filed on Dec. 28, 2000.

(30) **Foreign Application Priority Data**

Dec. 20, 2000 (DE) 100 63 435

(51) **Int. Cl.**
A61K 31/517 (2006.01)
C07D 239/94 (2006.01)
C07D 413/02 (2006.01)

(52) **U.S. Cl.** **514/266.22**; 514/266.4; 514/266.24; 514/217.06; 514/313; 514/314; 544/293; 544/122; 544/283; 544/284

(58) **Field of Classification Search** 514/266.24, 514/266.4; 544/293
See application file for complete search history.

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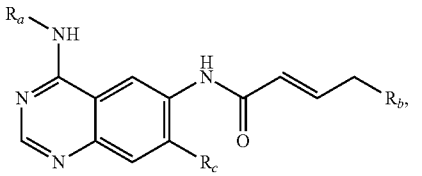
(57) **ABSTRACT**

A compound of general formula I



(I)

wherein:

R_a is a benzyl, 1-phenylethyl, or 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl) amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl) amino group; and

R_c is a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a tautomer, stereoisomer, or salt thereof,

particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, in particular an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in the treatment of diseases, especially tumoral diseases and diseases of the lungs and airways, and the preparation thereof.

7 Claims, No Drawings

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QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

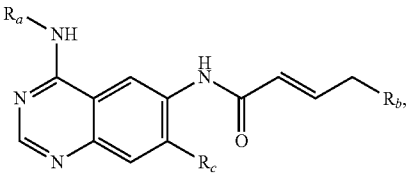
Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

RELATED APPLICATIONS

Benefit under 35 U.S.C. §119(e) of prior provisional application Ser. No. 60/259,201, filed [Dec. 18, 2000] *Dec. 28, 2000*, is hereby claimed*; benefit under 35 U.S.C. §119 of German application 100 63 435.4 filed Dec. 20, 2000 is also claimed*.

SUMMARY OF THE INVENTION

The present invention relates to quinazoline derivatives of general formula



(I)

the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, the use thereof for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract, and the preparation thereof.

In the above general formula I

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R_b denotes a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl) amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy or tetrahydropyran-4-ylmethoxy group,

with the exception of the compounds

(1) 3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline and

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline.

Preferred compounds of the above general formula I are those wherein

R_a, R_b, and R_c are as hereinbefore defined, but with the exception of the compounds

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-1-yl]amino}-7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-1yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-3-yloxy)quinazoline,

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydropyran-4-yloxy)quinazoline,

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-2-ylmethoxy)quinazoline and

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

the tautomers, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

R_a denotes a 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R_b denotes a dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl) amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group and

R_c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy or tetrahydropyran-4-ylmethoxy group,

with the exception of the compounds

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclobutyloxyquinazoline,

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(8) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(9) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}7-cyclopropylmethoxyquinazoline,

(10) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(11) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline,

(12) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(13) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(15) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-ethyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline,

(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)oxy]quinazoline,

(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(21) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(25) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-3-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydropyran-4-yl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclobutyloxyquinazoline,

(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-3-yloxy)quinazoline,

(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydropyran-4-yloxy)quinazoline,

(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-(tetrahydrofuran-2-ylmethoxy)quinazoline,

(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(R)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline and

(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[(S)-N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino]-1-oxo-2-buten-1-yl}-amino)-7-cyclobutyloxyquinazoline,

the tautomers, the stereoisomers and the salts thereof.

The following particularly preferred compounds of general formula I may be mentioned by way of example:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline;

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline,

(c) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-bis(2-methoxyethyl)amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline,

(d) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-ethylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(e) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(f) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(g) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydrofuran-3-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline,

(h) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydrofuran-3-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)quinazoline,

(k) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)quinazoline,

(l) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(m) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline,

(o) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}7-[(tetrahydrofuran-3-yl)methoxy]quinazoline,

(p) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}7-cyclopropylmethoxyquinazoline,

(q) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

(r) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline,

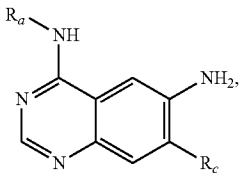
(s) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline; and

(t) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline,

the tautomers, the stereoisomers and the salts thereof.

The compounds of general formula I may be prepared by the following methods, for example:

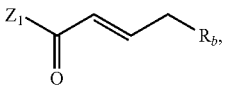
a) reacting a compound of general formula



(II)

wherein:

R_a and R_c are as hereinbefore defined, with a compound of general formula



(III)

wherein:

R_b is as hereinbefore defined; and

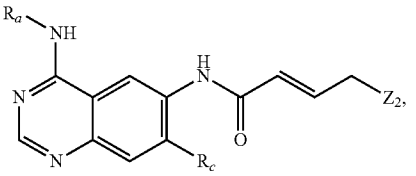
Z_1 denotes a leaving group such as a halogen atom, e.g., a chlorine or bromine atom, or a hydroxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of an inorganic or organic base and optionally in the presence of a dehydrating agent, expediently at temperatures between −50° C. and 150° C., preferably at temperatures between −20° C. and 80° C.

With a compound of general formula III wherein Z_1 denotes a leaving group, the reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 4-dimethylaminopyridine, in the presence of N-ethyldiisopropylamine (Hünig base), whilst these organic bases may simultaneously also act as solvent, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution, expediently at temperatures between −50° C. and 150° C., preferably at temperatures between −20° C. and 80° C.

With a compound of general formula III wherein Z_1 denotes a hydroxy group, the reaction is preferably carried out in the presence of a dehydrating agent, e.g., in the presence of isobutyl chloroformate, thionyl chloride, trimethyl chlorosilane, phosphorus trichloride, phosphorus pentoxide, hexamethyldisilazane, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, 1-hydroxybenzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently in a solvent such as methylene chloride, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulfoxide, ethylene glycol diethylether or sulfolane and optionally in the presence of a reaction accelerator such as 4-dimethylaminopyridine at temperatures between −50° C. and 150° C., but preferably at temperatures between −20° C. and 80° C.

b) Reacting a compound of general formula



(IV)

wherein:

R_a and R_c are as hereinbefore defined; and

Z_2 denotes a leaving group such as a halogen atom, a substituted hydroxy or sulfonyloxy group such as a chlorine or bromine atom, a methanesulfonyloxy or p-toluenesulfonyloxy group, with a compound of general formula:

(V)

wherein R_b is as hereinbefore defined.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, chlorobenzene, dimethylformamide, dimethylsulfoxide, methylene chloride, ethylene glycol monomethylether, ethylene glycol diethylether or sulfolane or mixtures thereof, optionally in the presence of an inorganic or tertiary organic base, e.g., sodium carbonate or potassium hydroxide, a tertiary organic base, e.g., triethylamine or N-ethyldiisopropylamine (Hünig base), whilst these organic bases may simultaneously also serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide at temperatures between −20° C. and 150° C., but preferably at temperatures between −10° C. and 100° C. The reaction may, however, also be carried out without a solvent or in an excess of the compound of general formula V used.

In the reactions described above, the secondary amino group bound to the quinazoline of general formula II or IV may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction. Examples of protecting groups include the formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl, or 2,4-dimethoxybenzyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g., in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulfuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g., in the presence of iodotrimethylsilane, at temperatures between 0° C. and 120° C., preferably at temperatures between 10° C. and 100° C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example hydrogenolytically, e.g., with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0° C. and 100° C., but preferably at ambient temperatures between 20° C. and 60° C., and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert-butyl or tert-butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50° C. and 120° C. or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0° C. and 50° C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf N. L. Allinger and E. L. Eliel in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g., by chromatography and/or fractional crystallization, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallization from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as, e.g., esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g., on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are, e.g., the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (−)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (−)-menthyloxycarbonyl.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

The compounds of general formulae II to V used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature.

For example, a starting compound of general formula II is obtained by reacting a 7-fluoro-6-nitro compound correspondingly substituted in the 4 position with a corresponding alkoxide and subsequently reducing the nitro compound thus obtained or

a starting compound of general formula III is obtained, for example, by reacting a suitable bromocrotonic acid derivative with one of the amines of general formula V known from the literature, or

a starting compound of general formula IV is obtained by acylating a compound of general formula II with a suitable crotonic acid derivative.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R), whilst this may be achieved for example by inhibiting ligand bonding, receptor dimerization or tyrosine kinase itself. It is also possible to block the transmission of signals to components located further down.

The biological properties of the new compounds were investigated as follows:

The inhibition of human EGF-receptor kinase was determined using the cytoplasmic tyrosine kinase domain (methionine 664 to alamine 1186, based on the sequence published in Nature 309 (1984), 418). To do this, the protein was expressed in Sf9 insect cells as a GST fusion protein using the Baculovirus expression system.

The enzyme activity was measured in the presence or absence of the test compounds in serial dilutions. The polymer pEY (4:1) produced by SIGMA was used as the substrate. Biotinylated pEY (bio-pEY) was added as the tracer substrate. Every 100 μl of reaction solution contained 10 μl of the inhibitor in 50% DMSO, 20 μl of the substrate solution (200 mM HEPES pH 7.4, 50 mM magnesium acetate, 2.5 mg/ml poly(EY), 5 μg/ml bio-pEY) and 20 μl of enzyme preparation. The enzyme reaction was started by the addition of 50 μl of a 100 μM ATP solution in 10 mM magnesium chloride. The dilution of the enzyme preparation was adjusted so that the incorporation of phosphate into the bio-pEY was linear in terms of time and quantity of enzyme. The enzyme preparation was diluted in 20 mM HEPES pH 7.4, 1 mM EDTA, 130 mM common salt, 0.05% Triton X-100, 1 mM DTT and 10% glycerol.

The enzyme assays were carried out at ambient temperature over a period of 30 minutes and were ended by the addition of 50 μl of a stopping solution (250 mM EDTA in 20 mM HEPES pH 7.4). 100 μl were placed on a streptavidin-coated microtiter plate and incubated for 60 minutes at ambient temperature. Then the plate was washed with 200 μl of a washing solution (50 mM Tris, 0.05% Tween 20). After the addition of 100 μl of a HRPO-labelled anti-PY antibody (PY20H Anti-PTyr:HRP produced by Transduction Laboratories, 250 ng/ml), it was incubated for 60 minutes. Then the microtiter plate was washed three times with 200 μl of washing solution. The samples were then combined with 100 μl of a TMB-peroxidase solution (A:B=1:1, Kirkegaard Perry Laboratories). After 10 minutes, the reaction was stopped. The extinction was measured at $OD_{450\ nm}$ with an ELISA reader. All data points were measured three times.

The data were matched by means of an iterative calculation using an analytical program for sigmoidal curves (Graph Pad Prism Version 3.0) with variable Hill pitch. All the iteration data released showed a correlation coefficient of more 0.9 and the upper and lower values of the curves showed a spread of at least a factor of 5. The concentration of active substance which inhibits the activity of EGF-receptor kinase by 50% (IC_{50}) was derived from the curves.

The following results were obtained:

Compound (Example No.)	Inhibition of EGF-Receptor Kinase IC_{50} [nM]
1	0.7
1(2)	0.6
1(3)	4.0
1(5)	3.0
1(10)	0.5
1(22)	1.0
1(32)	0.3
1(33)	0.5
1(34)	0.4

The compounds of general formula I according to the invention thus inhibit signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosine kinases. These are, e.g., benign or malignant tumors, particularly tumors of epithelial and neuroepithelial origin, metastasization and the abnormal proliferation of vascular endothelial cells (neoangiogenesis).

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, e.g., in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasis, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases, such as may be found, e.g., in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Menetrier's disease, secreting adenomas and protein loss syndrome.

In addition, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat other diseases caused by abnormal function of tyrosine kinases, such as, e.g., epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of hematopoietic cells, etc.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g., etoposide), mitosis inhibitors (e.g., vinblastine), compounds which interact with nucleic acids (e.g., cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g., tamoxifen), inhibitors of metabolic processes (e.g., 5-FU etc.), cytokines (e.g., interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or anti-inflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion. These combinations may be administered either simultaneously or sequentially.

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g., with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it.

Preparation of the Starting Compounds

EXAMPLE I

3-methylaminotetrahydrofuran

3.43 g of lithium aluminium hydride are added batchwise to 50 ml of tetrahydrofuran while cooling with an ice bath. Then a solution of 5.00 g of 3-[(benzyloxycarbonyl)-amino] tetrahydrofuran in 20 ml tetrahydrofuran is added dropwise, while the temperature remains below 10° C. After 10 minutes, the cooling bath is removed and the reaction mixture is refluxed for about three hours. For working up, 3.7 ml of water, 3.7 ml of 15% sodium hydroxide solution, and another 3 ml of water are carefully added dropwise to the reaction mixture while cooling with an ice bath. Then some tetrahydrofuran is added and the mixture is stirred for another 15 minutes. The aluminium hydroxide slurry precipitated is suction filtered and washed with a total of 150 ml of tetrahydrofuran. The filtrate is evaporated down using the rotary evaporator. A colorless oil remains, which is reacted without any further purification. Mass spectrum (ESI^+): m/z=102 $[M+H]^+$; R_f value: 0.20 (silica gel, methylene chloride/methanol=9:1).

EXAMPLE II

3-[(benzyloxycarbonyl)amino]tetrahydrofuran

12.36 ml of tetrahydrofuran-3-carboxylic acid and 27.84 ml of diphenylphosphorylazide in 500 ml of dioxane are combined with 41.91 g of benzyl alcohol and 35.81 ml of triethylamine. The reaction mixture is heated to 100° C. for about seven hours. After cooling to ambient temperature, the reaction mixture is evaporated down using the rotary evaporator. The residue is taken up in 500 ml of methylene chloride and washed twice with 100 ml of 1 N sodium hydroxide solution. The organic phase is dried over magnesium sulfate and evaporated down. The crude product is purified by chromatography over a silica gel column with cyclohexane/ethyl acetate (3:1 to 1:2) as eluant. Yield: 15.60 g (55% of theory); mass spectrum (ESI^-): m/z=220 $[M-H]^-$; R_f value: 0.78 (silica gel, methylene chloride/methanol=9:1).

EXAMPLE III

6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-((R)-tetrahydrofuran-3-yloxy)quinazoline

A mixture of 12.80 g of 4-[(3-chloro-4-fluorophenyl) amino]-6-nitro-7-((R)-tetrahydrofuran-3-yloxy)quinazoline, 200 ml of ethanol, 100 ml of water, and 17.20 ml of glacial acetic acid is heated to reflux temperature. Then a total of 7.00 g of iron powder is added in batches. The reaction mixture is

refluxed for about four hours and then cooled to ambient temperature overnight. For working up, the reaction mixture is evaporated using the rotary evaporator. The residue is taken up in methylene chloride/methanol (9:1), mixed with 20 ml of concentrated ammonia solution and filtered through a layer of silica gel. It is washed with copious amounts of methylene chloride/methanol (9:1) and the combined filtrates are evaporated down. The residue is stirred with diethylether and suction filtered. Yield: 8.59 g (73% of theory); mass spectrum (ESI^-): m/z=373, 375 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

The following compounds are obtained analogously to Example III:

(1) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-((S)-tetrahydrofuran-3-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=373, 375 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

(2) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(tetrahydropyran-4-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.20 (silica gel, ethyl acetate).

(3) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.55 (silica gel, ethyl acetate/methanol=9:1).

(4) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=387, 389 $[M-H]^-$; R_f value: 0.40 (silica gel, ethyl acetate/methanol=9:1).

EXAMPLE IV

4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-((R)-tetrahydrofuran-3-yloxy)quinazoline

13.80 g of potassium tert-butoxide are added batchwise to a solution of 10.80 g of (R)-3-hydroxytetrahydrofuran in 100 ml of N,N-dimethylformamide while cooling with an ice bath. The reaction mixture is stirred for about one hour, then 10.40 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-fluoroquinazoline are added batchwise. The cooling bath is then removed and the deep red reaction mixture is stirred for two hours at ambient temperature. For working up the reaction mixture is poured onto about 500 ml of water and neutralized with 2 N hydrochloric acid. The yellowish precipitate formed is suction filtered and dried at 70° C. in a circulating air drier. Yield: 12.80 g; melting point: 244° C.; mass spectrum (ESI^-): m/z=403, 405 $[M-H]^-$.

The following compounds are obtained analogously to Example IV:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-((S)-tetrahydrofuran-3-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=403, 405 $[M-H]^-$; R_f value: 0.45 (silica gel, ethyl acetate).

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-(tetrahydropyran-4-yloxy)quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.42 (silica gel, ethyl acetate).

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.47 (silica gel, ethyl acetate).

(4) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI^-): m/z=417, 419 $[M-H]^-$; R_f value: 0.41 (silica gel, ethyl acetate).

(5) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=433, 435 $[M+H]^+$; R_f value: 0.79 (silica gel, ethyl acetate/methanol=9:1).

(6) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=419, 421 $[M+H]^+$; R_f value: 0.44 (silica gel, ethyl acetate).

(7) 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI^+): m/z=419, 421 $[M+H]^+$; R_f value: 0.44 (silica gel, ethyl acetate).

EXAMPLE V

(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamine

21.10 g of (R)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine (crude product from Example VI) are dissolved in 200 ml of methanol and hydrogenated in the presence of 4.00 g of palladium on activated charcoal (10% Pd) at ambient temperature until the uptake of hydrogen has ended. For working up the catalyst is filtered off and the filtrate is evaporated using the rotary evaporator. A thin yellow oil is left, which is further reacted without any more purification. Yield: 8.60 g (73% of theory); mass spectrum (ESI^+): m/z=116 $[M+H]^+$.

The following compounds are obtained analogously to Example V:

(1) (S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamine
Mass spectrum (ESI^+): m/z=116 $[M+H]^+$.

(2) N-[(tetrahydropyran-4-yl)methyl]-N-methylamine
Mass spectrum (ESI^+): m/z=130 $[M+H]^+$.

EXAMPLE VI

(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine

A solution of 24.60 g of (R)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide in 90 ml tetrahydrofuran is added dropwise to 17.00 g of lithium aluminium hydride in 150 ml of tetrahydrofuran. The reaction mixture is refluxed for two hours. For working up it is cooled to 0° C. in an ice bath, mixed with 20 ml of water and 10 ml of 15 N sodium hydroxide solution and stirred for another 20 minutes. Then it is filtered through a layer of magnesium sulfate and washed with a total of about 500 ml of tetrahydrofuran. The filtrate is evaporated down in vacuo, leaving a yellowish oil which is further reacted without any more purification. Yield: 21.10 g (92% of theory); mass spectrum (ESI^+): m/z=206 $[M+H]^+$.

The following compounds are obtained analogously to Example VI:

(1) (S)-N-[(tetrahydrofuran-2-yl)methyl]-N-benzyl-N-methylamine
R_f value: 0.20 (silica gel, ethyl acetate/methanol=9:1).

(2) N-[(tetrahydropyran-4-yl)methyl]-N-benzyl-N-methylamine
Mass spectrum (ESI^+): m/z=220 $[M+H]^+$.

EXAMPLE VII

(R)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide

25.30 g of N-benzyl-N-methylamine are added to a solution of 20.00 ml of (R)-tetrahydrofuran-2-carboxylic acid in 200 ml tetrahydrofuran. Then a total of 67.10 g of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate are added batchwise while cooling with an ice bath and

the reaction mixture is then stirred for about 48 hours at ambient temperature. The precipitate formed is suction filtered, the filtrate is evaporated, mixed with water and filtered again. The filtrate obtained is made alkaline with sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water and saturated sodium chloride solution, dried over magnesium sulfate, and evaporated down. A yellowish oil remains, which is further reacted without any further purification. Yield: 24.60 g (54% of theory); mass spectrum (ESI^+): m/z=220 $[M+H]^+$; R_f value: 0.62 (silica gel, ethyl acetate).

The following compounds are obtained analogously to Example VII:

(1) (S)-tetrahydrofuran-2-carboxylic acid-N-benzyl-N-methylamide

Mass spectrum (ESI^+): m/z=242 $[M+Na]^+$; R_f value: 0.62 (silica gel, ethyl acetate).

(2) tetrahydropyran-4-carboxylic acid-N-benzyl-N-methylamide

The amide coupling is carried out with 1,1'-carbonyldiimidazole in tetrahydrofuran. Mass spectrum (ESI^+): m/z=256 $[M+Na]^+$; R_f value: 0.45 (silica gel, ethyl acetate).

EXAMPLE VIII

6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydropyran-4-yl)methoxy]quinazoline

22.80 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-nitro-7-[(tetrahydropyran-4-yl)methoxy]quinazoline are hydrogenated in 300 ml of tetrahydrofuran in the presence of 3.50 g of platinum dioxide at ambient temperature until the calculated amount of hydrogen has been taken up. The catalyst is filtered off and the filtrate is evaporated to dryness using the rotary evaporator. The residue is stirred with diethylether, suction filtered, washed with diethylether and dried at ambient temperature. Yield: 19.95 g (93% of theory); mass spectrum (ESI^+): m/z=403, 405 $[M+H]^+$; melting point: 221° C.

The following compounds are obtained analogously to Example VIII:

(1) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=389, 391 $[M+H]^+$; R_f value: 0.11 (silica gel, ethyl acetate).

(2) 6-Amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=389, 391 $[M+H]^+$; R_f value: 0.33 (silica gel, ethyl acetate/methanol=9:1).

Preparation of the Final Compounds

EXAMPLE 1

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

4.70 ml of oxalyl chloride are added dropwise to a solution of 4.50 g of bromocrotonic acid in 60 ml of methylene chloride. Then one drop of N,N-dimethylformamide is added. After about 30 minutes, the development of gas has ended and the reaction mixture is evaporated using the rotary evaporator. The crude bromocrotonic acid chloride is taken up in 30 ml of methylene chloride and, while cooling with an ice bath, added dropwise to a solution of 7.00 g of 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline and 10.20 ml of Hünig base in 150 ml of tetrahydrofuran. The reaction mixture is stirred for about 1.5 hours while cooling with an ice bath and then for another two hours at ambient temperature. Then 5.20 g of N-(2-methoxyethyl)-N-methylamine are added and the reaction mixture is stirred overnight at ambient temperature. For working up, it is diluted with methylene chloride and washed thoroughly with water. The organic phase is dried over magnesium sulfate and evaporated down. The crude product is purified by chromatography over a silica gel column with ethyl acetate followed by ethyl acetate/methanol (19:1) as eluant. Yield: 5.07 g (51% of theory); mass spectrum (ESI^-): m/z=512, 514 $[H-H]^-$; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).

The following compounds are obtained analogously to Example 1:

(1) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxyquinazoline

Mass spectrum (ESI^-): m/z=468, 470 $[M-H]^-$; R_f value: 0.09 (silica gel, ethyl acetate/methanol=9:1).

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline

Mass spectrum (ESI^-): m/z=482, 484 $[M-H]^-$; R_f value: 0.11 (silica gel, ethyl acetate/methanol=9:1).

(3) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-bis(2-methoxyethyl)amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=532 $[M-H]^-$; R_f value: 0.40 (silica gel, ethyl acetate/methanol=9:1).

(4) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-ethylamino]-1-oxo-2-buten-1yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=502 $[M-H]^-$; R_f value: 0.20 (silica gel, ethyl acetate/methanol=9:1).

(5) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=488 $[M-H]^-$; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).

(6) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=514 $[H-H]^-$; R_f value: 0.15 (silica gel, ethyl acetate/methanol=9:1).

(7) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N-(tetrahydrofuran-3-yl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=500 $[M-H]^-$; R_f value: 0.18 (silica gel, ethyl acetate/methanol=9:1).

(8) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydrofuran-3-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

Mass spectrum (ESI^-): m/z=538, 540 $[M-H]^-$; R_f value: 0.27 (silica gel, ethyl acetate/methanol=9:1).

(9) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)quinazoline; mass spectrum (ESI^+): m/z=486, 488 $[M+H]^+$.

(10) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)quinazoline

Mass spectrum (ESI^+): m/z=486, 488 $[M+H]^+$; R_f value: 0.45 (silica gel, methylene chloride/methanol=5:1).

(11) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)quinazoline

Mass spectrum (ESI^+): m/z=500, 502 $[M+H]^+$; R_f value: 0.55 (silica gel, methylene chloride/methanol=5:1).

(12) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

Mass spectrum (ESI^+): m/z=500, 502 $[M+H]^+$; R_f value: 0.60 (silica gel, methylene chloride/methanol=5:1).

(13) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; R_f value: 0.50 (silica gel, methylene chloride/methanol=5:1).
(14) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.31 (silica gel, ethyl acetate/methanol=9:1).
(15) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=446 [M+H]+; R_f value: 0.11 (silica gel, ethyl acetate/methanol=9:1).
(16) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=588, 590 [M+H]+; R_f value: 0.55 (silica gel, methylene chloride/methanol=9:1).
(17) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=542, 544 [M+H]+; R_f value: 0.55 (silica gel, methylene chloride/methanol=9:1).
(18) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxyethyl)-N-methylamino]-1oxo-2-buten-1-yl}amino)-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.25 (silica gel, ethyl acetate/methanol=9:1).
(19) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=540, 542 [M+H]+; melting point: 149° C.-153° C.
(20) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=540, 542 [M+H]+; R_f value: 0.29 (silica gel, ethyl acetate/methanol=9:1).
(21) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=560 [M+H]+; R_f value: 0.17 (silica gel, ethyl acetate/methanol=9:1).
(22) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI−): m/z=508, 510 [M−H]−; melting point: 140° C.
(23) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=496, 498 [M+H]+; R_f value: 0.42 (silica gel, ethyl acetate/methanol=9:1).
(24) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; melting point: 141° C.
(25) 4-[(R)-(1-phenylethyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline
Mass spectrum (ESI+): m/z=530 [M+H]+; R_f value: 0.32 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(26) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(R)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; melting point: 117° C.-121° C.
(27) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{(S)-N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=554, 556 [M+H]+; R_f value: 0.32 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(28) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=514, 516 [M+H]+; R_f value: 0.19 (silica gel, methylene chloride/methanol/conc. aqueous ammonia=95:5:0.05).
(29) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=554, 556 [M−H]−; melting point: 174° C.
(30) 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydropyran-4-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=602, 604 [M+H]+; melting point: 100° C.-102° C.
(31) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; melting point: 110° C.-112° C.
(32) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; R_f value: 0.23 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.1).
(33) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-ethyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=500, 502 [M+H]+; melting point: 154° C.-157° C.
(34) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=514, 516 [M+H]+; R_f value: 0.34 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:1).
(35) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; melting point: 184° C.-185° C.
(36) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxyquinazoline
Mass spectrum (ESI+): m/z=512, 514 [M+H]+; R_f value: 0.53 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:0.5).
(37) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-ethyl-N-methylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=512, 514 [M−H]−; R_f value: 0.15 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia=90:10:1).
(38) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI−): m/z=526, 528 [M−H]−; R_f value: 0.27 (silica gel, methylene chloride/methanol=9:1).
(39) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-isopropyl-N-methylamino)-1-oxo-2-butene-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]quinazoline
Mass spectrum (ESI+): m/z=528, 530 [M+H]+; R_f value: 0.31 (silica gel, methylene chloride/methanol=9:1).

The following compounds may also be prepared analogously to the foregoing Examples and other methods known from the literature:

(1) 4-benzylamino-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxyquinazoline

(2) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(tetrahydropyran-4-yl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

(3) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydropyran-4-yl)methoxy]quinazoline

(4) 4-[(R)-(1-phenylethyl)amino]-6-[(4-{N-[(tetrahydrofuran-2-yl)methyl]-N-methylamino}1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline

(5) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

(6) 4-[(R)-(1-phenylethyl)amino]-6-({4-[N,N-bis(2-methoxyethyl)amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

(7) 4-[(R)-(1-phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]quinazoline

EXAMPLE 2

Coated tablets containing 75 mg of active substance

1 tablet core contains:	
active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape. Weight of core: 230 mg; die: 9 mm, convex. The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax. Weight of coated tablet: 245 mg.

EXAMPLE 3

Tablets containing 100 mg of active substance

Composition: 1 tablet contains:	
active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Preparation

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50° C., it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets. Weight of tablet: 220 mg; diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

EXAMPLE 4

Tablets containing 150 mg of active substance

Composition: 1 tablet contains:	
active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45° C., are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture. Weight of tablet: 300 mg; die: 10 mm, flat.

EXAMPLE 5

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:	
active substance	50.0 mg
corn starch (dried)	approx. 80.0 mg
lactose (powdered)	approx. 87.0 mg
magnesium stearate	3.0 mg
	approx. 420.0 mg

Preparation

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules. Capsule filling: approx. 320 mg; capsule shell: size 1 hard gelatine capsule.

EXAMPLE 6

Suppositories containing 150 mg of active substance

1 suppository contains:	
active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation

After the suppository mass has been melted, the active substance is homogeneously distributed therein and the melt is poured into chilled molds.

EXAMPLE 7

Suspension containing 50 mg of active substance	
100 ml of suspension contains:	
active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavoring	0.30 g
dist. water	ad 100 ml

Preparation

The distilled water is heated to 70° C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution, and the flavoring have been added and dissolved, the suspension is evacuated with stirring to eliminate air. 5 ml of suspension contains 50 mg of active substance.

EXAMPLE 8

Ampoules containing 10 mg active substance	
Composition:	
active substance	10.0 mg
0.01N hydrochloric acid	q.s.
double-distilled water	ad 2.0 ml

Preparation

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

EXAMPLE 9

Ampoules containing 50 mg of active substance	
Composition:	
active substance	50.0 mg
0.01N hydrochloric acid	q.s.
double-distilled water	ad 10.0 ml

Preparation

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

EXAMPLE 10

Capsules for powder inhalation containing 5 mg of active substance	
1 capsule contains:	
active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg). Weight of capsule: 70.0 mg; size of capsule: 3.

EXAMPLE 11

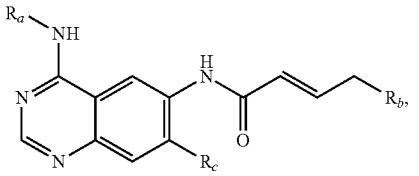
Solution for inhalation for hand-held nebulizers containing 2.5 mg active substance	
1 spray contains:	
active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid	q.s.
ethanol/water (50/50)	ad 15.000 mg

Preparation

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulizers (cartridges). Contents of the container: 4.5 g.

We claim:

1. A compound of formula I



(I)

wherein

R_a is a [benzyl, 1-phenylethyl, or] 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino[, N-methyl-N-ethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino] group; and

R_c is a [cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy,] tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a stereoisomer or physiologically acceptable salt thereof.

[**2**. The compound of claim **1**, wherein Rb is a dimethylamino or a stereoisomer or physiologically acceptable salt thereof.]

[**3**. The compound of formula I according to claim **1**, wherein:

R_a is a 1-phenylethyl or 3-chloro-4-fluorophenyl group;

R_b is a dimethylamino, N-methyl-N-ethylamino, N-methyl-N-isopropylamino, N-methyl-N-cyclopropylamino, N-methyl-N-(2-methoxyethyl)amino, N-ethyl-N-(2-methoxyethyl)amino, bis(2-methoxyethyl)amino, morpholino, N-methyl-N-(tetrahydrofuran-3-yl)amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)amino, N-methyl-N-(tetrahydrofuran-3-ylmethyl)amino, N-methyl-N-(tetrahydropyran-4-yl)amino, or N-methyl-N-(tetrahydropyran-4-ylmethyl)amino group; and

R_c is a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetradrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a stereoisomer or physiologically acceptable salt thereof.]

[**4**. The compounds of claim **3**, wherein

R_b is a dimethylamino,

or a stereoisomer or physiologically acceptable salt thereof.]

[**5**. The compounds of claim **3**, wherein

R_a is a 3-chloro-4-fluorohenyl group and

R_b is a dimethylamino group,

or a stereoisomer or physiologically acceptable salt thereof.]

[**6**. The compound of formula I according to claim **1**, wherein:

R_a is a 3-chloro-4-fluorophenyl group;

R_b is a dimethylaminno group; and

R_c is a tetrahydrofuran-3-yloxy, tetrahydrofuran-2-ylmethoxy, tetrahydrofuran-3-ylmethoxy, tetrahydropyran-4-yloxy, or tetrahydropyran-4-ylmethoxy group,

or a steroisomer or physiologically acceptable salt thereof.]

7. The compound of claim 1, wherein:

R_c is a tetrahydrofuran-3-yloxy,

or a steroisomer or physiologically acceptable salt thereof.

8. 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-(tetrahydrofuran-3-yl)oxy)quinazoline.

9. A physiologically acceptable salt comprising the combination of the compound according to claim 8 with an organic or inorganic acid.

10. The salt according to claim 9 wherein the acid is hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

11. The salt according to claim 10, wherein the acid is maleic acid.

12. 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-(tetrahydrofuran-3-yl)oxy)quinazoline.

* * * * *

EXHIBIT B

US008426586B2

(12) United States Patent
Soyka et al.

(10) Patent No.: US 8,426,586 B2
(45) Date of Patent: Apr. 23, 2013

(54) **PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS**

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(73) Assignee: **Boehringer Ingelheim International GmbH**, Ingelheim am Rhein (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1851 days.

(21) Appl. No.: **11/457,622**

(22) Filed: **Jul. 14, 2006**

(65) **Prior Publication Data**

US 2007/0027170 A1 Feb. 1, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/941,116, filed on Sep. 15, 2004, now abandoned.

(60) Provisional application No. 60/517,777, filed on Nov. 6, 2003.

(30) **Foreign Application Priority Data**

Oct. 17, 2003 (DE) 103 49 113

(51) **Int. Cl.**
C07D 239/84 (2006.01)
C07D 215/44 (2006.01)

(52) **U.S. Cl.**
USPC **544/153**; 546/153

(58) **Field of Classification Search** 544/153; 546/153
See application file for complete search history.

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Primary Examiner — Paul V. Ward
(74) *Attorney, Agent, or Firm* — Michael P. Morris; Anthony P. Bottino

(57) **ABSTRACT**

An improved process for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and related aminocrotonyl compounds and the preparation of a suitable salt of 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline for use as a pharmaceutically active substance.

11 Claims, 2 Drawing Sheets

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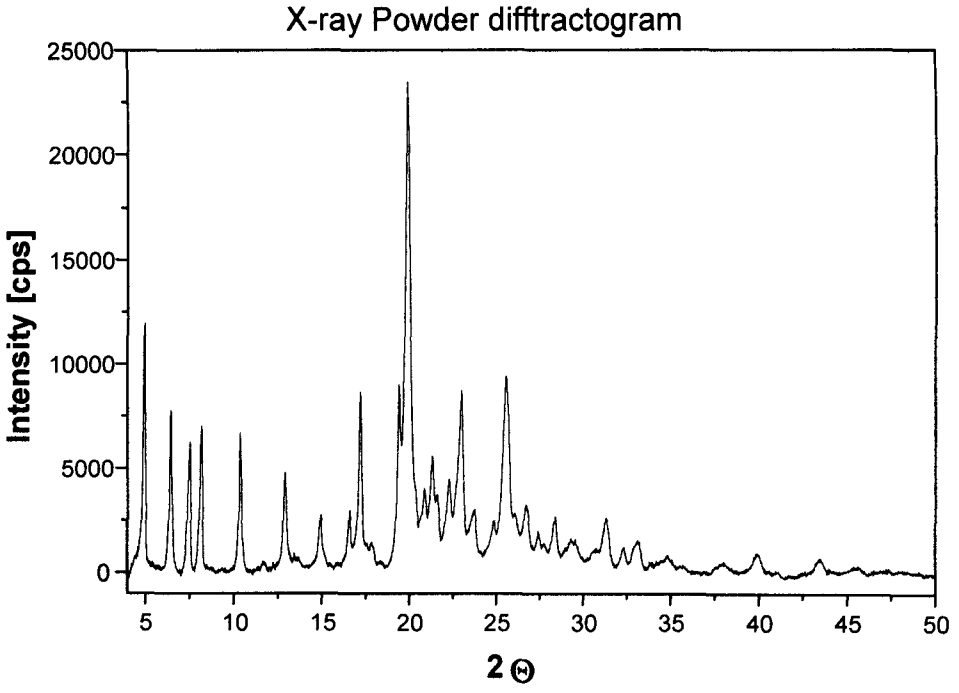
X-ray Powder difftractogram
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20000
15000
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10
15
20
25
30
35
40
45
50
2Θ

FIG. 1

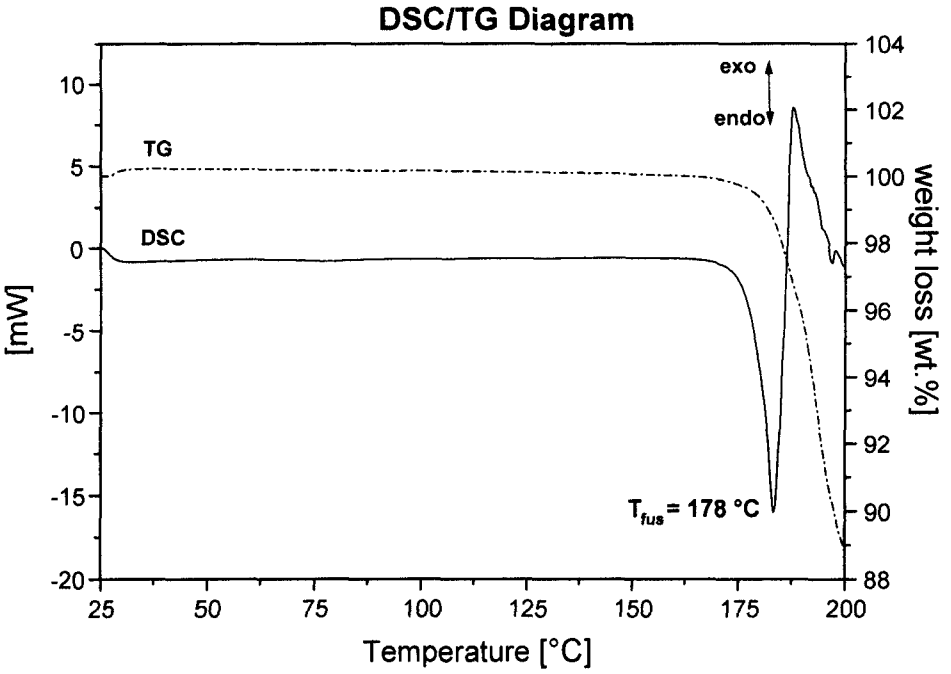

DSC/TG Diagram
exo
endo
TG
DSC
[mW]
weight loss [wt.%]
T_{fus} = 178 °C
Temperature [°C]
10
5
0
-5
-10
-15
-20
104
102
100
98
96
94
92
90
88
25
50
75
100
125
150
175
200

FIG. 2

PROCESS FOR PREPARING AMINO CROTONYL COMPOUNDS

RELATED APPLICATIONS

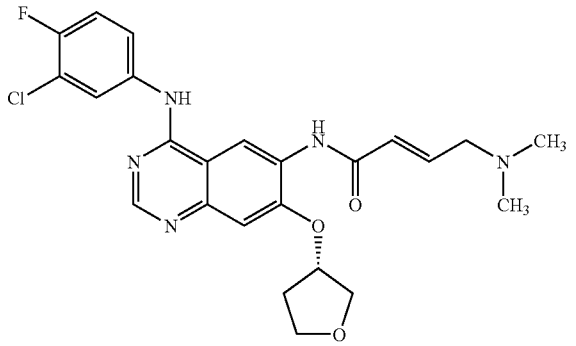
This application is a continuation of U.S. Ser. No. 10/941,116, filed Sep. 15, 2004, which in turn claimed benefit of U.S. Ser. No. 60/517,777, filed Nov. 6, 2003, and priority from German Application No. 103 49 113.9, filed Oct. 17, 2003, each of which related applications is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to an improved process for preparing aminocrotonyl compounds such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and the physiologically acceptable salts thereof, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, as well as 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate and the use thereof for preparing pharmaceutical compositions.

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]-amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline has the following structure:

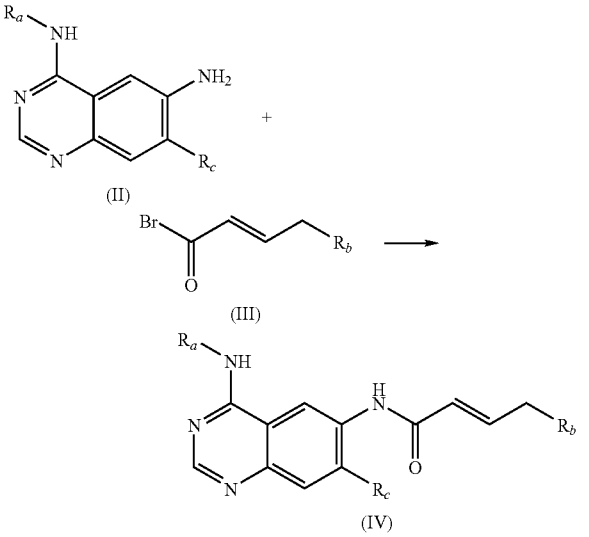
(I)



and is already known from WO 02/50043, which describes compounds with valuable pharmacological properties, including in particular an inhibiting effect on signal transduction mediated by tyrosinekinases and an inhibitory effect on signal transduction mediated by the Epidermal Growth Factor receptor (EGF-R). Therefore, compounds of this type are suitable for the treatment of diseases, particularly for the treatment of tumoral diseases, diseases of the lungs and respiratory tract and diseases of the gastrointestinal tract and bile duct and gall bladder.

WO 02/50043 discloses a method of preparation wherein aminocrotonyl compounds (IV) such as for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline are prepared in a one-pot reaction from the corresponding aniline component (II), bromocrotonic acid (III), oxalyl chloride and a secondary amine (see Diagram 1).

Diagram 1:



In this process the yield was at most 50%. In addition, purification was generally carried out by column chromatography. Therefore, the method of preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline was not suitable on an industrial scale. Furthermore, the method had the disadvantage that bromocrotonic acid is not commercially available in large amounts and also the corresponding methyl bromocrotonate is only available in a purity of approx. 80%. These circumstances also militate against the suitability of this process for the industrial production of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline.

In the light of the above disadvantages of the known method of production, the aim of the present invention is to provide a process which allows the production of aminocrotonylarylamides, particularly 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, using highly pure starting materials which are readily available and without any great technical expenditure. This new process should therefore also be suitable for synthesis on an industrial scale and hence for commercial application.

This aim is achieved by the process according to the invention for preparing 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline and other aminocrotonyl compounds. In addition to being industrially practicable with high yields the method of synthesis according to the invention also has the advantages of very good chemical purities and a low cis content of less than 0.1%.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an X-ray powder diffractogram of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate; and

FIG. **2** is a diagram depicting Thermoanalysis of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

In the process according to the invention the corresponding aminoaryl compound (V) is reacted with a di-(C_{1-4}-alkyl)-phosphonoacetic acid, preferably with diethylphosphonoacetic acid, in suitable solvents, after corresponding activation, preferably with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole or propanephosphonic anhydride, particularly preferably with 1,1-carbonyldiimidazole, according to Diagram 2. The solvent used may be for example tetrahydrofuran (THF), dimethylformamide (DMF) or ethyl acetate.

The activation may be carried out by any possible method of amide linking, i.e. for example with 1,1-carbonyldiimidazole, 1,1-carbonylditriazole, DCC(N,N-dicyclohexylcarbodiimide), EDC (N'-(dimethylaminopropyl)-N-ethylcarbodiimide), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), thiazolidine-2-thione or by conversion into the corresponding acid chloride, possibly using thionyl chloride. If desired the activation may be carried out using organic bases such as triethylamine or pyridine, while DMAP (dimethylaminopyridine) may additionally be added. Suitable solvents include DMF, THF, ethyl acetate, toluene, chlorinated hydrocarbons or mixtures thereof.

In the formulae that follow

X denotes a methyne group or a nitrogen atom,

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and

R^1 denotes a straight-chain or branched C_{1-4}-alkyl group.

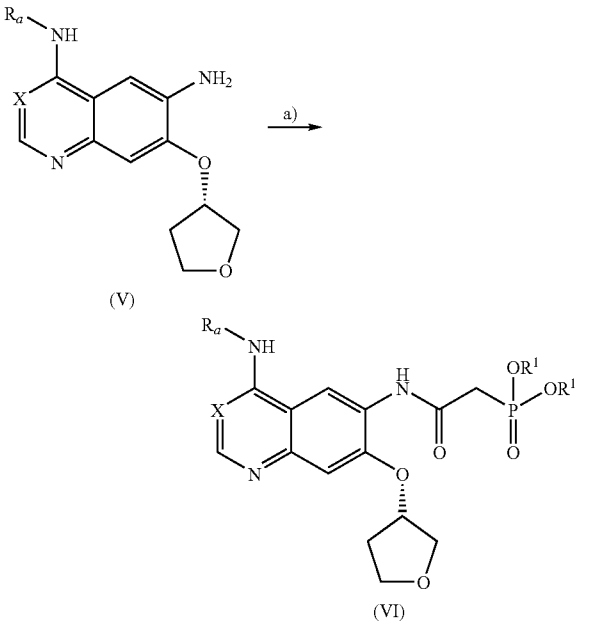
The process is preferably used for compounds wherein

X denotes a nitrogen atom,

R_a denotes a 3-chloro-4-fluorophenyl group and

R^1 denotes an ethyl group.

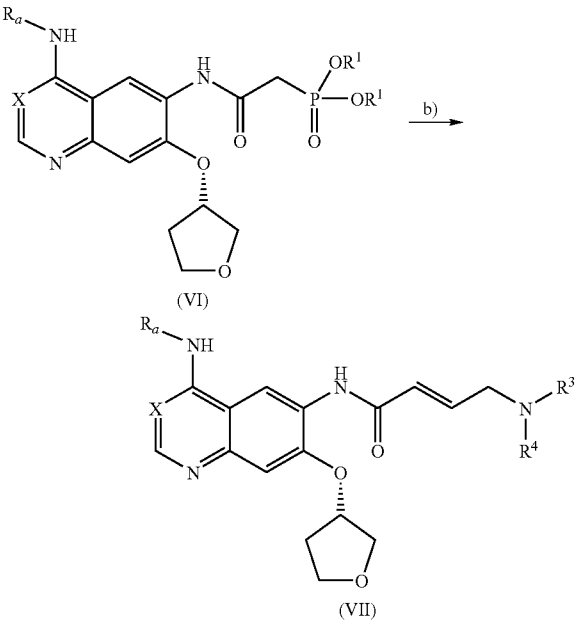
Diagram 2:



a) di-(C_{1-4}-alkyl)-phosphonoacetic Acid, Activating Agent

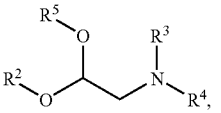
The arylamide (VI) thus obtained in a high yield and high purity is reacted with the corresponding 2-aminoacetaldehyde using suitable organic or inorganic bases in the sense of a Wittig-Horner-Emmons reaction (Diagram 3). This reaction may be carried out directly or after isolation of the compound (VI), for example by precipitation by the addition of tert-butylmethyl ether, for example. Suitable bases include for example DBU (1,5-diazabicyclo[4.3.0]non-5-ene), sodium hydroxide and potassium hydroxide, of which sodium hydroxide and potassium hydroxide are preferred and potassium hydroxide is particularly preferred. Instead of the aldehyde a corresponding equivalent, e.g. a hydrate or acetal, may be used, from which the aldehyde is released (beforehand or in situ).

Diagram 3:



b) Aldehyde, Base, THF/Water

The acetals used may be for example compounds of the following general type:



wherein R^2 to R^5 in each case represent a straight-chain or branched C_1-C_4-alkyl group, while the groups may be identical or different.

Preferably

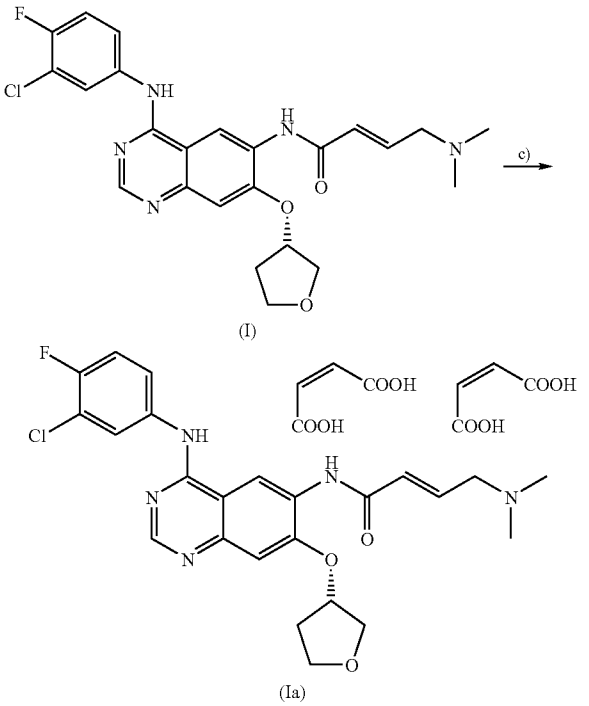
R^3 and R^4 in each case represent a methyl group and

R^2 and R^5 in each case represent an ethyl group.

The aminocrotonylarylamide of formula (VII) thus obtained, for example 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of formula (I), may then be converted into the salts thereof, particularly the physiologically acceptable salts thereof, by methods known per se. Preferably they are converted into fumarates, tartrates or maleates. The dimaleate of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline of structural formula (Ia) and the conversion of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into its dimaleate as shown in Diagram 4 are particularly preferred. To do this the compound (I) is dissolved in a suitable solvent, such as for example methanol, isopropanol, n-butanol or ethanol, optionally with the addition of water, preferably ethanol, and combined with crystalline maleic acid or a maleic acid solution, with heating. When ethanol is used as solvent the work is preferably done at a

temperature of between 60 and 75° C. using an ethanolic maleic acid solution. The reaction conditions are preferably selected so that the desired salt crystallises out as quickly as possible. Preferably approx. 2 equivalents of maleic acid are used. After crystallisation has set in the mixture is cooled to ambient temperature, stirred and the crystals consisting of compound (Ia) are separated off.

Diagram 4:



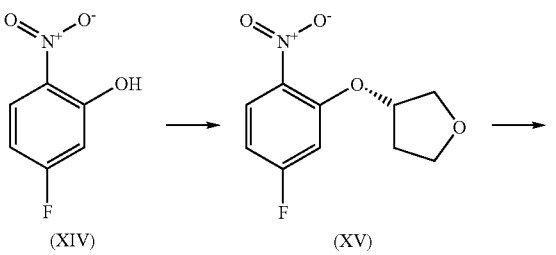
c) Maleic Acid, Ethanol

The starting compound of formula (V) may for example be prepared as follows in accordance with methods known from the literature.

The quinoline components of formula (V), wherein X═CH, may be obtained starting from commercially obtainable 3-fluoro-6-nitrophenol (XIV) by alkylation, exchanging the fluorine atom for an amino group and reacting with ethoxyacrylic acid esters, ethoxymethylene-cyanoacetic acid esters or ethoxymethylene-malonic acid esters (Diagram 5a).

The compound thus obtained (XVII) is then converted into the compound (XVIII) as described in Diagram 6 for the quinazoline analogue

Diagram 5a:



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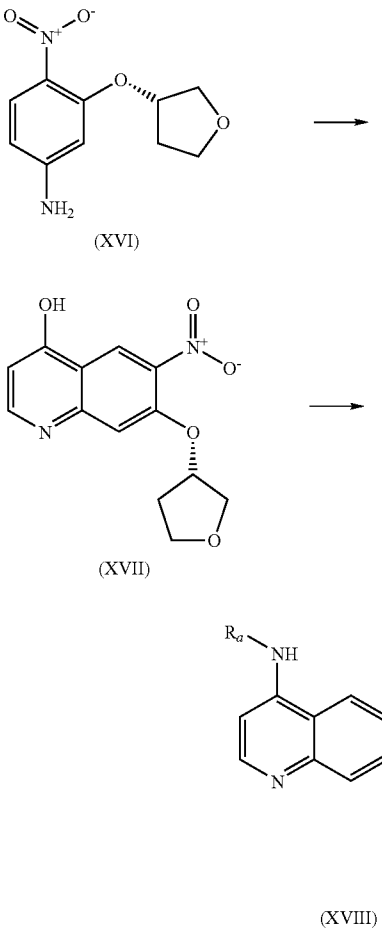
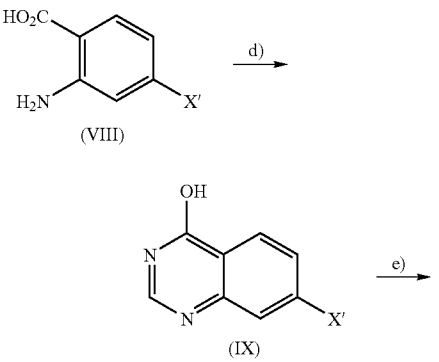


To prepare the compound (V) wherein X=N the following procedure is used:

Starting from commercially obtainable 4-chloro-anthranilic acid (VIII; X'=Cl) the quinazolinone (IX) is obtained by reaction with formamidine-acetate, and is then nitrogenated using sulphuric acid and concentrated nitric acid (Diagram 5b). Alternatively, 4-fluoro-anthranilic acid may also be used as the starting material.

Diagram 5b:



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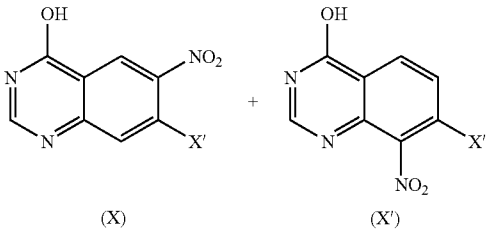
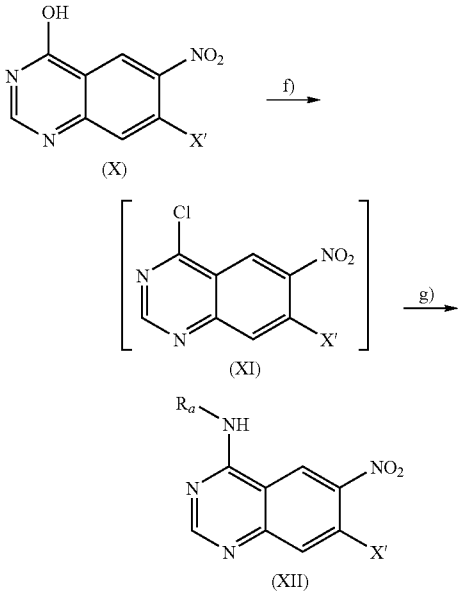


(X) (X′)

a: X′ = Cl
b: X′ = F
d) formamidine-acetate
e) H_2SO_4, HNO_3 conc.

The desired regioisomer (X) of the nitrogenation products thus obtained is then chlorinated, and the chlorination product (XI) is reacted in situ with the corresponding amine (Diagram 6).

Diagram 6:

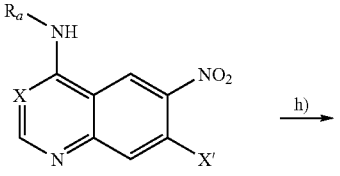


(X) (XI) (XII)

f) $SOCL_2$, acetonitrile
g) R_aNH_2

The compound of formula (XII) thus obtained is reacted with (S)-(+)-3-hydroxytetrahydrofuran to form compound (XIII). Hydrogenation of compound (XIII) or compound (XVIII) from Diagram 5a then yields the starting compound (V) (diagram 7).

Diagram 7:



(XII): X = N, X′ = Cl, F

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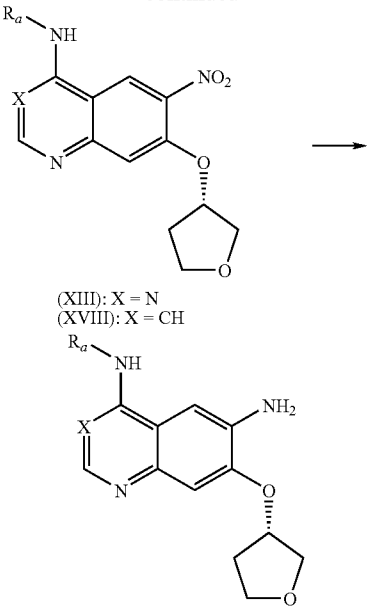


(XIII): X = N
(XVIII): X = CH

(V)

h) (S)-(+)-3-hydroxy-tetrahydrofuran
i) H_2

The invention also relates to 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate. This salt is particularly suitable for pharmaceutical use as it exists in only one crystalline modification, which is moreover anhydrous and very stable.

For pharmaceutical use an active substance not only has to exhibit the desired activity, but must also conform to additional requirements in order to be allowed to be used as a pharmaceutical composition. These parameters are to a large extent connected with the physicochemical nature of the active substance.

Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the pharmaceutical compositions should therefore have a high stability which must be guaranteed even under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in pharmaceutical formulations might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g. by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way. Preferably a pharmaceutically active substance should therefore have only limited hygroscopicity.

As the crystal modification of an active substance is important to the reproducible active substance content of a preparation, there is a need to clarify as far as possible any existing polymorphism of an active substance present in crystalline form. If there are different polymorphic modifications of an active substance care must be taken to ensure that the crystalline modification of the substance does not change in the pharmaceutical preparation later produced from it. Otherwise, this could have a harmful effect on the reproducible potency of the drug. Against this background, active substances characterised by only slight polymorphism are preferred.

Another criterion which may be of exceptional importance under certain circumstances depending on the choice of formulation or the choice of manufacturing process is the solubility of the active substance. If for example pharmaceutical solutions are prepared (e.g. for infusions) it is essential that the active substance should be sufficiently soluble in physiologically acceptable solvents. It is also very important for drugs which are to be taken orally that the active substance should be sufficiently soluble.

The problem of the present invention is to provide a pharmaceutically active substance which not only is characterised by high pharmacological potency but also satisfies the above-mentioned physicochemical requirements as far as possible. This problem is solved by 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethyl-amino)-1-oxo-2-buten-1-yl] amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]-amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate has a melting point of 178° C. (cf. the thermoanalysis shown in FIG. **2**). The crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate was investigated further by X-ray powder diffraction. The diagram obtained is shown in FIG. **1**.

The following Table lists the data obtained in this analysis:

TABLE

X-ray powder reflections and intensities (standardised) of the 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate

2-Θ [°]	d-value [Å]	intensity I/I_o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.467	1
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5

In the preceding Table the value "2Θ[°]" denotes the angle of diffraction in degrees and the value "d_{hkl} [Å]" denotes the specified distances in Å between the lattice planes.

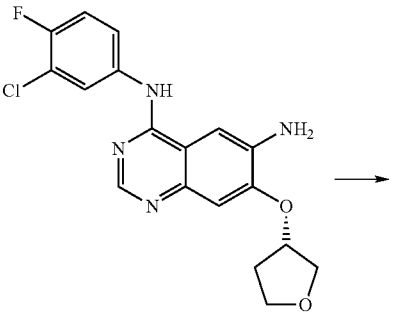
The x-ray powder diagrams were recorded, within the scope of the present invention, using a Bruker D8 Advanced diffractometer fitted with a PSD detector and a Cu anode as the x-ray source (CuK_{α_1} radiation, λ=1.5418 Å, 40 kV, 40 mA).

The following Examples are intended to illustrate the invention:

EXAMPLES

Example 1

Diethyl {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate



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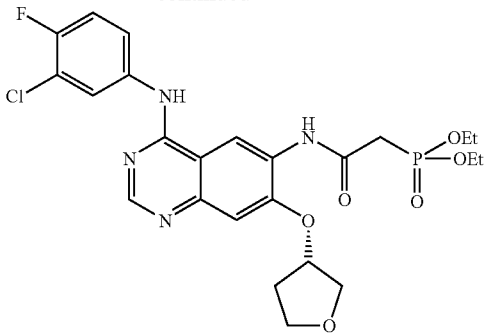


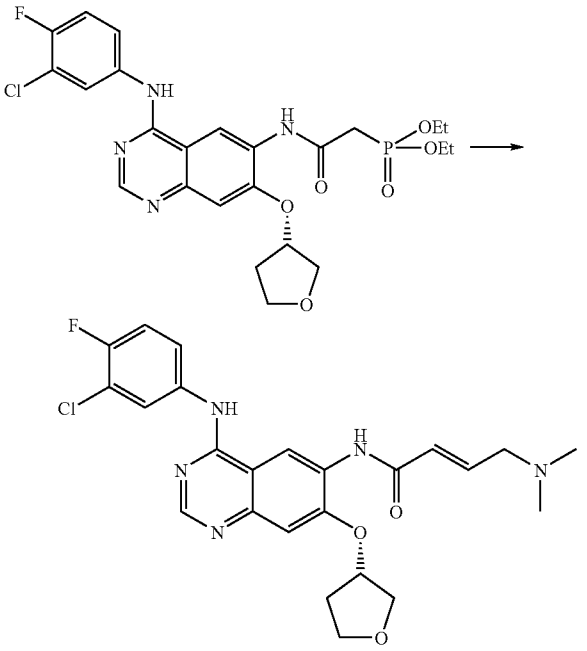
3.58 kg of 1,1-carbonyldiimidazole (22.16 mol) are placed in 12.8 liters of tetrahydrofuran and at 40° C. combined with 4.52 kg (22.16 mol) of diethylphosphonoacetic acid dissolved in 6.5 liters of tetrahydrofuran. The mixture is stirred for 30 minutes at 40° C. The resulting solution is referred to as solution A.

6.39 kg (17.05 mol) of N^4-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine are placed in 26.5 liters of tetrahydrofuran and at 40° C. combined with solution A and stirred for 2 hours at 30° C. 64 liters of tert.-butylmethylether are added to the suspension and after cooling to 20° C. the precipitate is removed by centrifuging. It is washed with a mixture of 16 liters of tetrahydrofuran and 16 liters of tert.-butylmethylether and then with 32 liters of water and dried at 50° C.

Yield: 6.58 kg (69.8%) of white crystals, content: HPLC 99.1 Fl %

Example 2

(E)-4-dimethylamino-but-2-enoic acid-[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6yl]-amide



5.6 liters of 30% hydrochloric acid (53.17 mol) are added to 4.4 liters of water. Then 4.28 kg of 95% (dimethylamino)-acetaldehyde-diethylacetal (26.59 mol) are added dropwise

within 20 minutes at 30° C. The reaction solution is stirred for 8 hours at 35° C. stirred, cooled to 5° C. and stored under argon. This solution is referred to as solution B.

4.55 kg (68.06 mol) of potassium hydroxide are dissolved in 23.5 liters of water and cooled to −5° C. This solution is referred to as solution C.

5.88 kg (10.63 mol) of diethyl ((4-(3-chloro-4-fluoro-phenylamino)-7-(tetrahydrofuran-3-yloxy)-quinazoline-6-yl-carbamoyl)-methyl)-phosphonate and 0.45 kg of lithium chloride (10.63 mol) are placed in 23.5 liters of tetrahydrofuran and cooled to −7° C. The cold solution C is added within 10 minutes. Then solution B is added at −7° C. within 1 hour. After stirring for a further hour at −5° C. the reaction mixture is heated to 20° C. and combined with 15 liters of water. After cooling to 3° C. the suspension is suction filtered, the precipitate is washed with water and dried. Yield: 5.21 kg of crude product, 100%, water content: 6.7%

The crystallisation of the crude product is carried out with butyl acetate/methylcyclohexane

Yield: 78% purity HPLC 99.4 Fl %, water content 5.4%

Example 3

(E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetra-hydrofuran-3-yloxy)-quinazolin-6yl)-amide dimaleate

6.0 kg (12.35 mol) of (E)-4-dimethylamino-but-2-enoic acid-(4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-yl)-amide are placed in 84 litres of ethanol and heated to 70° C. and combined with a solution of 2.94 kg (25.31 mol) of maleic acid in 36 liters of ethanol. After crystallisation has set in, first the mixture is cooled to 20° C. and stirred for 2 hours, then for 3 hours at 0° C. The precipitate is suction filtered, washed with 19 liters of ethanol and dried in vacuo at 40° C.

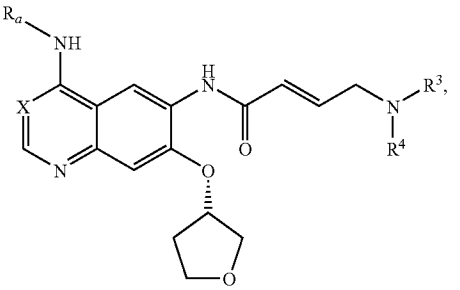
Yield: 8.11 kg (91.5%)

Melting point: 178° C.

^{1}H-NMR (CD_3OD): δ=2.47+2.27 (m+m, 2H), 2.96 (s, 6H), 4.03 (m, 2H), 4.07+3.92 (m+m, 2H), 4.18+4.03 (m+m, 2H), 5.32 (m, 1H), 6.26 (s, 4H), 6.80 (m, 1H), 6.99 (m, 1H), 7.27(s, 1H), 7.30 (t, 1H), 7.66 (m, 1H), 7.96 (dd, 1H), 8.62 (s, 1H), 9.07 (s, 1H) ppm

What is claimed is:

1. A process for preparing a compound of the formula (VII)



(VII)

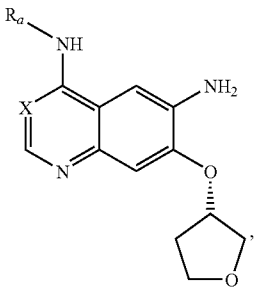
wherein X denotes a methyne group or a nitrogen atom,

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and

R^3 and R^4 denote a straight-chain or branched C_{1-4}-alkyl group,

comprising the following synthesis steps:

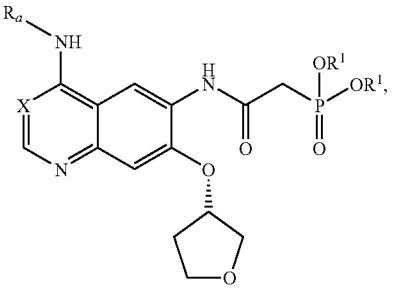
a) reacting a compound of the formula (V)



(V)

wherein X denotes a methyne group or a nitrogen atom and R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group, in suitable solvents after corresponding activation with di-(C_{1-4}-alkyl)-phosphonoacetic acid and

b) reacting the resulting compound of the formula (VI)

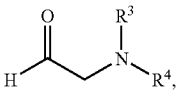


(VI)

wherein X denotes a methyne group or a nitrogen atom,

R_a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group and

R^1 denotes a straight-chain or branched C_{1-4}-alkyl group, with the aldehyde of formula



wherein R^3 and R^4 in each case represent a straight-chain or branched C_1-C_4-alkyl group, while the groups may be identical or different,

or a corresponding aldehyde equivalent, using suitable organic or inorganic bases.

2. A process for preparing 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl] amino}-7- ((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising the following synthesis steps:

a) reacting N^4-(3-chloro-4-fluoro-phenyl)-7-(tetrahydrofuran-3-yloxy)quinazoline-4,6-diamine in suitable solvents after corresponding activation with di-(C_{1-4}-alkyl)-phos -phonoacetic acid and

b) reacting the resulting dialkylester {[4-(3-chloro-4-fluoro-phenylamino)-7-((S)-tetrahydrofuran-3-yloxy)-quinazolin-6-ylcarbamoyl]-methyl}-phosphonate with the aldehyde prepared in situ from the corresponding (dimethylamino)-acetaldehyde-dialkylacetal using suitable organic or inorganic bases.

3. The process according to claim **2**, wherein in step a) diethylphosphonoacetic acid is used as reagent.

4. The process according to claim **1**, wherein in step b) DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene), sodium hydroxide or potassium hydroxide is used as base.

5. The process according to claim **4**, wherein in step b) potassium hydroxide is used as base.

6. A process for preparing the dimaleates of 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino }-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, comprising steps a and b according to claim **1** as well as the following step c):

c) converting the resulting 4-[(3-chloro-4-fluorophenyl) amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline into the dimaleate by reacting with maleic acid in a suitable solvent, with heating.

7. The process according to claim **6**, wherein ethanol or isopropanol is used as solvent, optionally with the addition of water.

8. The process according to claim **6**, wherein at least 2equivalents of maleic acid are used.

9. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S))-tetrahydofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using $CuK_{\alpha 1}$ radiation, λ=1.5418Å in the following table:

2-Θ [°]	intensity I/I_o [%]
4.91	47
6.42	33
7.47	27
8.13	30
10.37	30
17.19	36
19.43	38
19.91	100
21.33	21
22.94	32
25.56	37.

10. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using $CuK_{\alpha 1}$ radiation, λ=1.5418 Å in the following table:

2-Θ [°]	intensity I/I_o [%]
4.91	47
6.42	33
7.47	27
8.13	30
10.37	30
12.91	20
14.94	11
16.58	12
17.19	36
19.43	38
19.91	100
20.84	13
21.33	21

-continued

2-Θ [°]	intensity I/I_o [%]
21.58	12
22.25	15
22.94	32
25.56	37.

11. Crystalline 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S))-tetrahydofuran-3-yloxy)-quinazoline dimaleate, characterized by 2 Θ [°] values obtained by X-ray powder diffraction using $CuK_{\alpha 1}$ radiation, λ=1.5418 Å in the following table:

2-Θ [°]	d-value [Å]	intensity I/I_o [%]
4.91	18.0	47
6.42	13.8	33
7.47	11.8	27
8.13	10.9	30
10.37	8.53	30
11.69	7.56	2
12.91	6.85	20
13.46	6.58	3
13.66	6.48	2
14.94	5.93	11
16.58	5.34	12

-continued

2-Θ [°]	d-value [Å]	intensity I/I_o [%]
17.19	5.15	36
17.87	4.96	5
19.43	4.57	38
19.91	4.46	100
20.84	4.26	13
21.33	4.16	21
21.58	4.12	12
22.25	3.992	15
22.94	3.873	32
23.67	3.756	9
24.82	3.584	7
25.56	3.482	37
26.71	3.335	9
27.46	3.245	4
28.37	3.143	8
30.71	2.909	3
29.31	3.045	4
29.57	3.019	4
31.32	2.854	10
32.31	2.769	4
33.10	2.705	5
33.90	2.643	1
34.84	2.573	2
35.71	2.512	1
36.38	2.46	71
36.96	2.430	1
37.99	2.367	2
39.94	2.255	5.

* * * * *

EXHIBIT C

US009539258B2

(12) **United States Patent**
Solca et al.

(10) **Patent No.: US 9,539,258 B2**
(45) **Date of Patent: *Jan. 10, 2017**

(54) **QUINAZOLINE DERIVATIVES FOR THE TREATMENT OF CANCER DISEASES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/739,299**

(22) Filed: **Jun. 15, 2015**

(65) **Prior Publication Data**

US 2015/0272954 A1 Oct. 1, 2015

Related U.S. Application Data

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(30) **Foreign Application Priority Data**

Nov. 11, 2005 (EP) 05110656

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A61K 31/553	(2006.01)
A61K 33/24	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/517*** (2013.01); ***A61K 31/553*** (2013.01); ***A61K 33/24*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/517; A61K 31/553

See application file for complete search history.

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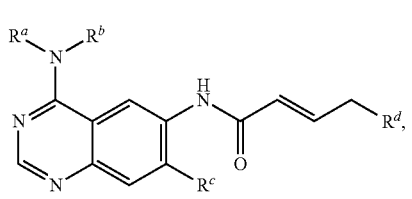
(57) **ABSTRACT**

The present invention relates to the use of quinazolines of formula (I),



(I)

wherein the groups R^a to R^d have the meanings given in the claims and specification, in cancer therapy.

5 Claims, 4 Drawing Sheets

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Figure 1: BIBW 2992 induces apoptosis in NCI-N87 gastric cancer cells

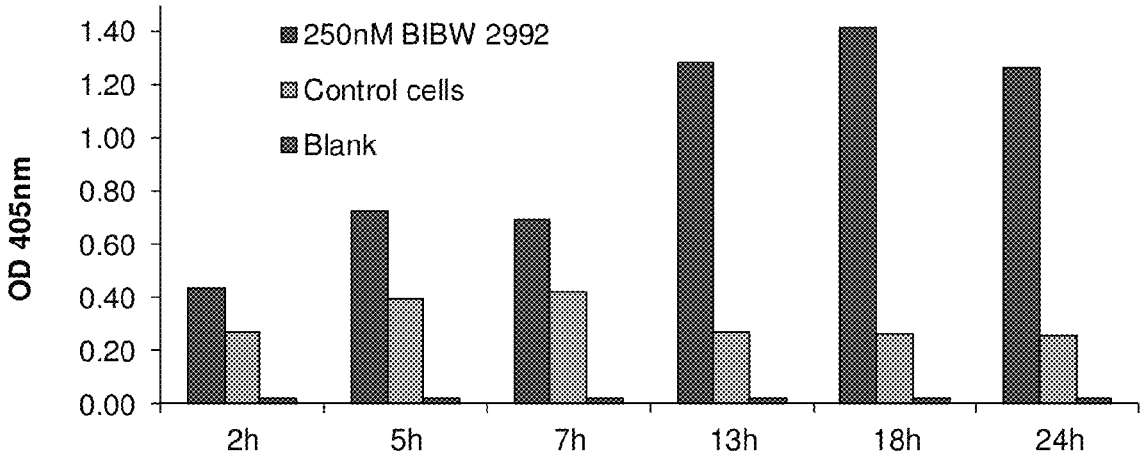


Figure 2: Effect of BIBW 2992 on the growth of preexisting HNSCC FaDu xenografts

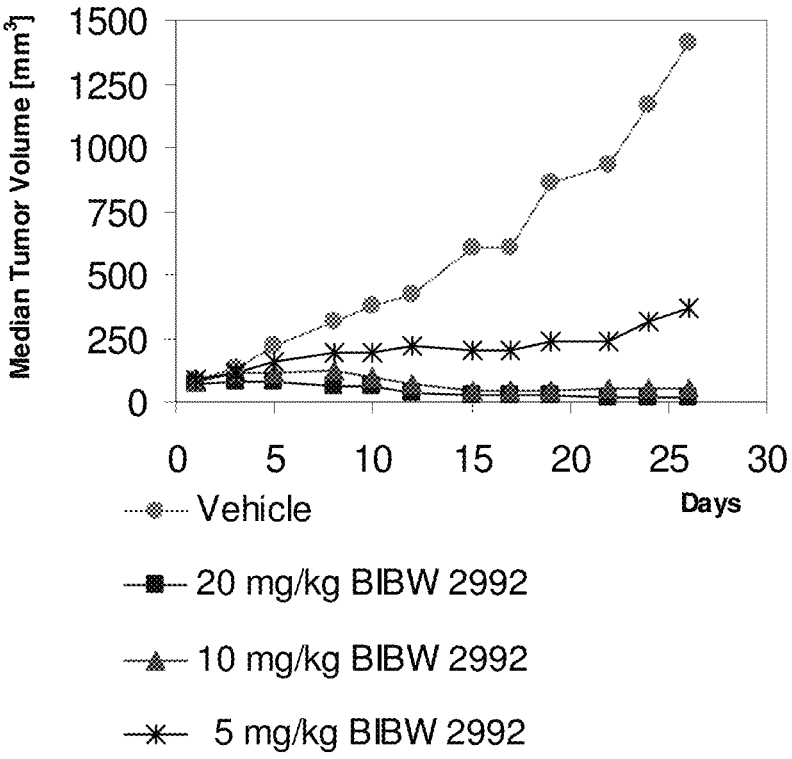
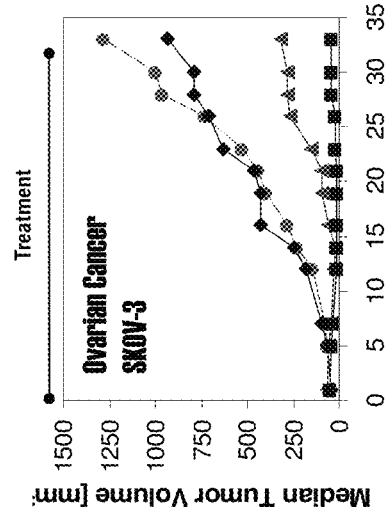


Figure 3: Effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts



compound	gefitinib	canertinib	BIBW 2992
Cmax [nM]	4181	674	83
$AUC_{(0\text{-}24h)}$ [nM*h]	41934	5066	972

compound	gefitinib	canertinib	BIBW 2992
Cmax [nM]	4737	359	236
$AUC_{(0\text{-}24h)}$ [nM*h]	62490	2803	2156

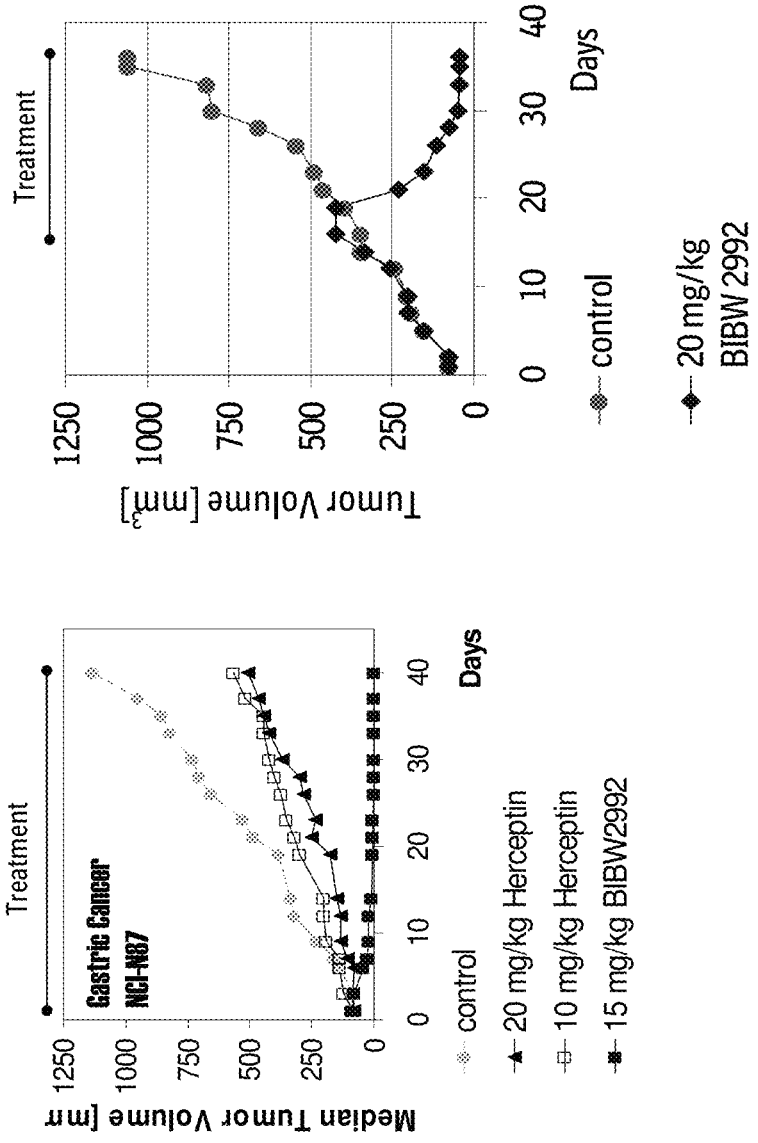
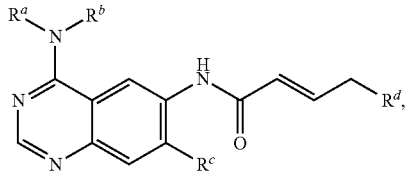


Figure 4: Effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts

QUINAZOLINE DERIVATIVES FOR THE TREATMENT OF CANCER DISEASES

The present invention relates to the use of quinazolines of formula (I),



(I)

wherein the groups R^a to R^d have the meanings given in the claims and specification, in cancer therapy.

BACKGROUND OF THE INVENTION

Compounds of formula (I) are disclosed in WO 02/50043, WO 2004/074263 and WO 2005/037824 as dual inhibitors of erbb1 receptor (EGFR) and erbB2 (Her2/neu) receptor tyrosine kinases, suitable for the treatment of e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastasisation and the abnormal proliferation of vascular endothelial cells (neoangiogenesis), for treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosine kinases, as well as for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosine kinases. The disclosure of WO 02/50043, WO 2004/074263 and WO 2005/037824 includes preparation as well as pharmaceutical formulations of the compounds and is incorporated by reference regarding these aspects. Furthermore, it is known for treatment of tumour diseases that the compounds may be used in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastine), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons) or antibodies.

SUMMARY OF THE INVENTION

It has been found that the compounds of formula (I) provide unexpected advantages in the treatment of cancer, e.g. superior efficacy and/or reduced side effects, especially in the treatment of several specific cancer-subindications.

A first aspect of the present invention therefore is a method of treating cancer, preferably the specific cancer-subindications referred to hereinafter, said method comprising administering a therapeutically effective amount of a compound of formula (I) to a patient in need thereof, optionally in combination with radiotherapy, radio-immunotherapy and/or tumour resection by surgery.

Any reference to a compound of formula (I) in connection with the invention should be understood to include the tautomers, racemates, enantiomers and diastereomers thereof, if any, the mixtures thereof as well as the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof.

The expression "patient" relates to a human or non-human mammalian patient suffering from cancer and thus in need of such treatment, preferably the patient is a human person. Furthermore, the expression "patient" should be understood to include such cancer patients carrying tumors with wild-type EGF receptor as well as pre-selected cancer patients

with tumors harboring activating EGFR mutations. These can be located in the tyrosine kinase domain of the EGF receptor such as for instance the L858R or L861 point mutations in the activation loop (exon 21), or in-frame deletion/insertion mutations in the ELREA sequence (exon 19), or substitutions in G719 situated in the nucleotide binding loop (exon 18). Additional activating mutations have been reported in the extracellular domain of the EGF receptor in various indications (e.g. EGFR vIII displaying exon 2-7 deletions). Other mutations such as the T790M point mutation in exon 20 as well as certain exon 20 insertions (e.g. D770_N771insNPG) which confer resistance to particular drugs should also be included, as well as double mutants such as the combined L858R/T790M mutation or the exon-19-del/T790M.

The expression "patient" should be understood to include also such cancer patients carrying tumors with wild-type HER2 receptor as well as pre-selected cancer patients with tumors harboring activating HER2 mutations, e.g. M774_A775insAYVM.

The indication "cancer" as used in the context of the invention is to be understood in a most general sense as a disease characterized by inappropriate cellular proliferation, migration, apoptosis or angiogenesis, preferably by inappropriate cellular proliferation. Inappropriate cell proliferation means cellular proliferation resulting from inappropriate cell growth, from excessive cell division, from cell division at an accelerated rate and/or from inappropriate cell survival.

"Radiotherapy" means administering ionizing radiation to the patient, as conventionally used in cancer therapy. Radiotherapy may be applied before, in parallel or after treatment by administration of a compound of formula (I).

"Tumour resection by surgery" is one standard option in cancer therapy and may be applied before or after treatment by administration of a compound of formula (I).

A second aspect of the present invention is directed to the use of a compound of formula (I) for the manufacture of a medicament for the treatment of cancer, preferably for the treatment of the specific cancer-subindications referred to hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: shows BIBW 2992 induces apoptosis in NCI-N87 gastric cancer cells.

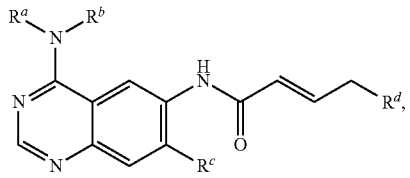
FIG. **2**: shows the effect of BIBW 2992 on the growth of preexisting HNSCC FaDu xenografts.

FIG. **3**: shows the effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts.

FIG. **4**: shows the effect of BIBW 2992 on the growth of MDA-MB-453 and SKOV-3 xenografts.

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment (1), both with regard to the first and second aspect of the invention, formula (I)



(I)

is defined to encompass those compounds wherein

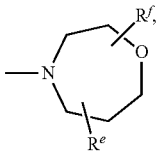
R^a denotes a benzyl, 1-phenylethyl or 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom or a C_{1-4}-alkyl group,

R^c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl-amino, N-cyclopropylmethyl-N-methyl-amino, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, N-(2-methoxyethyl)-N-methyl-amino, N-(1-methoxy-2-propyl)-N-methyl-amino, N-(3-methoxypropyl)-N-methyl-amino, pyrrolidino, 2-methylpyrrolidino, 2-(methoxymethyl)-pyrrolidino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, N-cyclopropyl-N-methyl-amino-, N-methyl-N-(tetrahydrofuran-3-yl)-amino, N-methyl-N-(tetrahydrofuran-2-ylmethyl)-amino, N-methyl-N-(tetrahydrofuran-3-yl-methyl)-amino, N-methyl-N(tetrahydropyran-4-yl)-amino or N-methyl-N-(tetrahydropyran-4-yl-methyl)-amino group, or a group of formula (II)

(II)

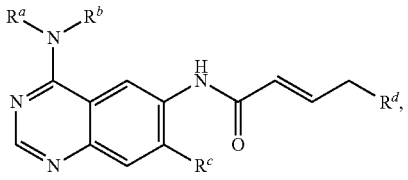


wherein R^e and R^f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

optionally in form of its tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally in form of the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof.

In a second embodiment (2), both with regard to the first and second aspect of the invention, formula (I)

(I)



is defined to encompass those compounds wherein

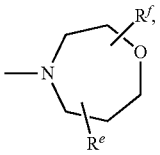
R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl-amino, N-cyclopropylmethyl-N-methyl-amino, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, N-(2-methoxyethyl)-N-methyl-amino, N-(1-methoxy-2-propyl)-N-methyl-amino, N-(3-methoxypropyl)-N-methyl-amino, pyrrolidino, 2-methylpyrrolidino, 2-(methoxymethyl)-pyrrolidino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, N-methyl-N-(tetrahydrofuran-3-yl)-amino, N-methyl-N-(tetrahydrofuran-2-yl-methyl)-amino, N-methyl-N-(tetrahydrofuran-3-yl-methyl)-amino, N-methyl-N-(tetrahydropyran-4-yl)-amino or N-methyl-N-(tetrahydropyran-4-yl-methyl)-amino group, or a group of formula (II)

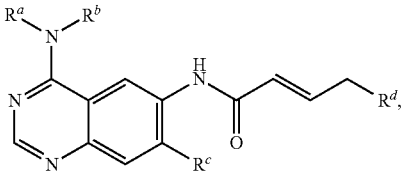
(II)



wherein R^e and R^f denote a hydrogen atom.

In a third embodiment (3), both with regard to the first and second aspect of the invention, formula (I)

(I)



is defined to encompass those compounds wherein

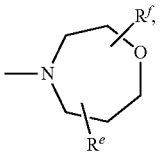
R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy, tetrahydrofuran-3-yl-methoxy, tetrahydropyran-4-yl-oxy or tetrahydropyran-4-yl-methoxy group,

R^d denotes a dimethylamino, N-cyclopropyl-N-methyl, N-ethyl-N-methyl-amino, N,N-diethylamino, N-isopropyl-N-methyl-amino, morpholino, (1S,4S)-2-oxa-5-aza-bicyclo-[2.2.1]hept-5-yl or (1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, group, or a group of formula (II)

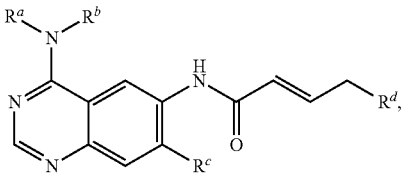
(II)



wherein R^e and R^f denote a hydrogen atom.

In a fourth embodiment (4), both with regard to the first and second aspect of the invention, formula (I)

(I)



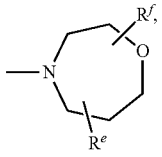
is defined to encompass those compounds wherein

R^a denotes a 3-chloro-4-fluorophenyl group,

R^b denotes a hydrogen atom,

R^c denotes a tetrahydrofuran-3-yl-oxy, tetrahydrofuran-2-yl-methoxy or tetrahydrofuran-3-yl-methoxy group,

R^d denotes a dimethylamino group or a group of formula (II)



(II)

wherein R^e and R^f, denote a hydrogen atom.

In a fifth embodiment (5), both with regard to the first and second aspect of the invention, formula (I) is defined to encompass the compounds selected from the group consisting of

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(l) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-ethyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(m) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-isopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(n) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(o) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(N,N-diethyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

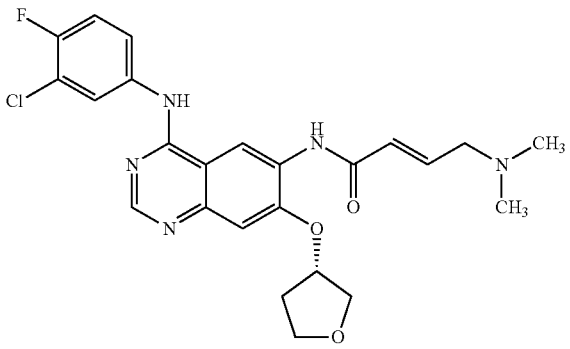
(p) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

(q) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((1R,4R)-2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline.

In a sixth embodiment (6), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,



(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

the dimaleate salt of compound (d) being especially preferred:

(d') 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

In a preferred embodiment the invention relates to the use of a compound of formula (I) according to the invention, wherein the disease is cancer selected from the group consisting of carcinomas, sarcomas, melanomas, myelomas, hematological neoplasias, lymphomas and childhood cancers.

Examples of carcinomas within the scope of the invention include but are not limited to adenocarcinoma (AC), squamous cell carcinoma (SCC) and mixed or undifferentiated carcinomas. Carcinomas within the scope of the invention include but are not limited to the following histologies:

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Central nervous system tumours: Astrocytoma, glioblastoma, meningeoma, neurinoma, schwannoma, ependymoma, hypophysoma, oligodendroglioma, medulloblastoma;
- Bronchial and mediastinal tumours:
  - Bronchial tumours:
    - Small cell lung cancers (SCLC): oat-cell lung cancer, intermediate cell cancer, combined oat-cell lung cancer;
    - Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC;
  - Mesothelioma;
  - Thymoma;

Thyroid carcinomas: papillary, follicular, anaplastic, medullary;
Tumours of the gastrointestinal tract:
Oesophageal cancers: SCC, AC, anaplastic, carcinoid, sarcoma;
Gastric cancers: AC, adenosquamous, anaplastic;
Colorectal cancers: AC, including hereditary forms of AC, carcinoid, sarcoma;
Anal cancers: SCC, transitional epithelial cancer, AC, basal cell carcinoma;
Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;
Hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, hepatoblastoma;
Biliary carcinomas: AC, SCC, small cell, undifferentiated;
Gastrointestinal stroma tumours (GIST);
Gynaecological cancers:
Breast cancers: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;
Ovarian cancers: Epithelial tumours, stroma tumours, germ cell tumours, undifferentiated tumours;
Cervical cancers: SCC, AC, mixed and undifferentiated tumours;
Endometrial cancers: AC, SCC, mixed, undifferentiated tumours;
Vulvar cancers: SCC, AC;
Vaginal cancers: SCC, AC;
Urinary tract and testicular cancers:
Testicular cancers: seminoma;
Non-seminomatous germ cell tumours: teratoma, embryonal cell carcinoma, choriocarcinoma, yolk sac tumour, mixed, Sertoli and Leydig-cell tumours;
Extragonadal germ cell tumours;
Prostate cancers: AC, small cell, SCC;
Renal cell cancers: AC, including clear cell, papillary and chromophobous carcinomas, hereditary forms (e.g. von-Hippel-Lindau syndrome), nephroblastoma;
Urinary bladder cancers: transitional cell (urothelial) cancers, SCC, AC;
Urethral cancers: SCC, transitional cell cancers, AC;
Penile cancers: SCC;
Tumours of endocrine tissue:
Thyroid cancers: papillary, follicular, anaplastic, medullary carcinomas, including MEN syndrome;
Tumours of the endocrine pancreas;
Carcinoids;
Pheochromocytoma.

Examples of sarcomas within the scope of the invention include but are not limited to Ewing-sarcoma, osteosarcoma or osteogenic sarcoma, chondrosarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, mesothelial sarcoma or mesothelioma, fibrosarcoma, angiosarcoma or hemangioendothelioma, liposarcoma, glioma or astrocytoma, myxosarcoma, malignant fibrous histiocytoma, mesenchymous or mixed mesodermal tumour, neuroblastoma and clear cell sarcoma.

Examples of melanomas within the scope of the invention include but are not limited to superficial spreading melanoma, nodular and lentigo-maligna melanoma.

Examples of myelomas within the scope of the invention include but are not limited to immunocytoma, plasmocytoma and multiple myeloma.

In another preferred embodiment the invention relates to the use according to the invention, wherein the hematological neoplasia is leukemia.

Further examples of hematologic neoplasias within the scope of the invention include but are not limited to acute or chronic leukemias of myeloid, erythroid or lymphatic origin, myelodysplastic syndromes (MDS) and myeloproliferative syndromes (MPS, such as chronic myelogeneous leukemia, osteomyelofibrosis, polycythemia vera or essential thrombocythemia).

Examples of lymphomas within the scope of the invention include but are not limited to:
Hodgkin's-lymphoma;
Non-Hodgkin's-lymphomas: T- and B-cell lymphomas
B-cell lymphomas:
Low and intermediate grade: Chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), small lymphocytic lymphoma, hairy cell leukemia, plasmacytoid lymphoma, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma including MALT-lymphoma;
High grade: diffuse large B-cell lymphoma (DLBCL including immunoblastic and centroblastic variants), lymphoblastic, Burkitt's lymphoma;
T-cell lymphomas:
Low grade: T-CLL, T-PLL, Mycosis fungoides, Sezary-syndrome;
High grade: Anaplastic large cell, T-immunoblastic and lymphoblastic.

In another preferred embodiment the invention relates to the use according to the invention, wherein the disease is cancer selected from the group consisting of mixed tumours, undifferentiated tumours and metastases thereof.

Examples of mixed tumours within the scope of the invention include but are not limited to adenosquamous carcinomas, mixed mesodermal tumours, carcinosarcomas and teratocarcinomas.

Examples of undifferentiated, other tumours or metastases thereof within the scope of the invention include but are not limited to undifferentiated tumours, carcinomas of unknown primary (CUP), metastases of unknown primary (MUP) and pheochromocytoma, carcinoids.

Additionally the following tumour diseases which can be treated with a compound of formula (I) in accordance with the invention are summarized:

acral lentiginous melanoma, actinic keratoses, adenoid cycstic carcinoma, adenomas, adenosarcoma, adrenocortical carcinoma, AIDS-related lymphoma, bartholin gland carcinoma, brain stem glioma, capillary carcinoma, central nervous system lymphoma, chondosarcoma, choriod plexus papilloma/carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, epitheloid, focal nodular hyperplasia, gastrinoma, gestational trophoblastic tumor, glucagonoma, hepatic adenoma, hepatic adenomatosis, hypopharyngeal cancer, hypothalamic and visual pathway glioma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, intraocular invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, laryngeal cancer, leukemia-related disorders, lip and oral cavity cancer, malignant mesothelial tumors, malignant thymoma, medulloepithelioma, merkel cell carcinoma, mucoepidermoid carcinoma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroepithelial adenocarcinoma, nodular

melanoma, oat cell carcinoma, oligodendroglial, oral cancer, oropharyngeal cancer, pineal cell, pituitary tumors, pseudosarcoma, pulmonary blastoma, parathyroid cancer, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma, retinoblastoma, serous carcinoma, small intestine cancer, soft tissue carcinomas, somatostatin-secreting tumor, supratentorial primitive neuroectodermal tumors, uveal melanoma, verrucous carcinoma, vipoma, Waldenstrom's macroglobulinemia, well differentiated carcinoma, and Wilm's tumor.

In a further preferred embodiment (7), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl) methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-methoxy-quinazoline,

and the cancer indication to be treated by administration of a compound of formula (I) is selected from the group consisting of

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Central nervous system tumours: Astrocytoma, glioblastoma, meningeoma, neurinoma, schwannoma, ependymoma, hypophysoma, oligodendroglioma, medulloblastoma;
- Bronchial and mediastinal tumours:
  - Bronchial tumours:
    - Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC;
  - Thyroid carcinomas: papillary, follicular, anaplastic, medullary;
- Tumours of the gastrointestinal tract:
  - Oesophageal cancers: SCC, AC, anaplastic;
  - Gastric cancers: AC, adenosquamous, anaplastic;
  - Colorectal cancers: AC, including hereditary forms of AC, carcinoid, sarcoma;
  - Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;
  - Hepatocellular cancers, cholangiocarcinoma
- Gynaecological cancers:
  - Breast cancers: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;
  - Ovarian cancers: Epithelial tumours, stroma tumours, germ cell tumours, undifferentiated tumours;
- Urinary tract and testicular cancers:
  - Prostate cancers: AC, small cell, SCC;
  - Renal cell cancers: AC, including clear cell, papillary and chromophobous carcinomas, hereditary forms (e.g. von-Hippel-Lindau syndrome), Wilm's tumor, nephroblastoma;
  - Urinary bladder cancers: transitional cell (urothelial) cancers, SCC, AC.

Examples of sarcomas within the scope of the invention include but are not limited to Ewing-sarcoma, osteosarcoma or osteogenic sarcoma, chondrosarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, mesothelial sarcoma or mesothelioma, fibrosarcoma, angiosarcoma or hemangioendothelioma, liposarcoma, glioma or astrocytoma, myxosarcoma, malignant fibrous histiocytoma, mesenchymous or mixed mesodermal tumour, neuroblastoma and clear cell sarcoma.

In a very preferred embodiment (8), both with regard to the first and second aspect of the invention, the compounds of formula (I) are selected from the group consisting of

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

the dimaleate salt of compound (d) being especially preferred:

(d') 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate (BIBW2992 MA_2),

and the cancer indication to be treated by administration of a compound of formula (I) is selected from the group consisting of

- Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;
- Colorectal cancers, metastatic or non-metastatic: AC, including hereditary forms of AC, carcinoid, sarcoma;
- Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;
- Breast cancers, metastatic or non-metastatic: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;
- Prostate cancers: AC, small cell, SCC;
- Gastric cancers: AC, adenosquamous, anaplastic;
- Ovarian cancer;

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC.

It is known that cancer patients carrying activating EGFR mutations in their tumors, i.e. within the tyrosine kinase domain of the EGF receptor, may show increased sensitivity to treatment with EGFR inhibitors. Analogously, cancer patients carrying activating HER2 mutations, e.g. M774_A775insAYVM, in their tumors may show increased sensitivity to treatment with HER2 inhibitors. Both groups of patients as well as a subgroup carrying both activating EGFR and HER2 mutations may show increased sensitivity to treatment with dual inhibitors of erbb1 receptor (EGFR) and erbB2 (Her2/neu).

The presence of specific gain-of-function mutations within the tyrosine kinase domain of the EGF receptor in a subgroup of NSCLC patients has been associated with increased sensitivity to treatment with gefitinib and erlotinib (Lynch, New England Journal Medicine 350, 2129 (2004); Paez, Science 304, 1497 (2004); Pao, Proceedings of the National Academy of Science of the United States 101, 13306 (2004)). In particular, the L858R point mutation (exon 21) as well as deletion/insertion mutations in the ELREA sequence (exon 19) account for the majority of gefitinib responders. A secondary point mutation in exon 20, T790M, is associated with acquired resistance to gefitinib or erlotinib. This mutation is analogous to the T315I mutation identified in CML patients who relapse under imatinib treatment (imatinib resistant patients).

Irreversible inhibitors (e.g., HKI-272 or CL 387,785), in contrast to reversible inhibitors (e.g., gefitinib), are able to inhibit proliferation and EGF-induced EGFR phosphorylation in cell lines expressing double mutant EGF receptors (Kwak, Proceedings of the National Academy of Science of the United States 102, 7665 (2005) and Kobayashi, New England Journal Medicine 352, 786 (2005)).

Any aspect of the present invention therefore includes, as a sub-aspect, optional pre-selection of cancer patients for an EGFR mutation in the tyrosine kinase domain of the EGF receptor as well as pre-selection of cancer patients for an HER2 mutation. The EGFR mutations preferably relevant in in this context are selected from the group consisting of the L858R and L861 point mutations in the activation loop (exon 21), in-frame deletion/insertion mutations in the ELREA sequence (exon 19), substitutions in G719 situated in the nucleotide binding loop (exon 18), activating mutations in the extracellular domain of the EGF receptor such as EGFR vIII displaying exon 2-7 deletions, the T790M point mutation in exon 20, exon 20 insertions such as D770_N771insNPG, and double mutants such as the combined L858R/T790M mutation and the exon-19-del/T790M. The HER2 mutation preferably relevant in in this context is the M774_A775insAYVM mutation.

Methods for detecting mutations in the tyrosine kinase domain of the EGF receptor are known in the art, several corresponding diagnostic tools are approved by the FDA and commercially available, e.g. an assay for the detection of epidermal growth factor receptor mutations in patients with non-small cell lung cancer (Genzyme Corp.; see also Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006: Abstract 10060).

Any of the embodiments of the invention mentioned hereinbefore defining compounds of formula (I) and cancer indications applies accordingly to the optional sub-aspect of pre-selection of cancer patients for an activating EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or pre-selection of cancer patients for an activating HER2 mutation. Treatment of EGFR mutant cancer patients with the compounds of formula (I) may allow a response in cancer patients with acquired or persistent resistance to gefitinib or erlotinib treatment. Treatment of cancer patients carrying an activating HER2 mutant in their tumors with the compounds of formula (I) may allow a responce in cancer patients with acquired or persistent resistance to certain chemotherapeutics such as e.g. lapatinib or herceptin.

Most preferred cancer indications with EGFR or HER2 mutations relevant in connection with the sub-aspect of patient pre-selection for mutations are selected from the group consisting of

Head and neck tumours: SCC, AC, transitional cell cancers, mucoepidermoid cancers, undifferentiated carcinomas;

Colorectal cancers, metastatic or non-metastatic: AC, including hereditary forms of AC, carcinoid, sarcoma;

Pancreatic cancers: AC, including ductal and acinary cancers, papillary, adenosquamous, undifferentiated, tumours of the endocrine pancreas;

Breast cancers, metastatic or non-metastatic: AC, including invasive ductal, lobular and medullary cancers, tubular, mucinous cancers, Paget-carcinoma, inflammatory carcinoma, ductal and lobular carcinoma in situ;

Prostate cancers: AC, small cell, SCC;

Gastric cancers: AC, adenosquamous, anaplastic;

Ovarian cancer;

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC,

but especially

Non-small cell lung cancers (NSCLC): SCC, spindle cell carcinoma, AC, bronchioalveolar carcinoma, large cell NSCLC, clear cell NSCLC, especially metastatic, second line patients who have failed at least one prior chemotherapy regimen or 3rd/4th line patients who have received Tarceva or Iressa for at least 12 weeks and then failed,

preferably to be treated by administration of a compound of formula (I) selected from the group consisting of:

(a) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclobutyloxy-quinazoline,

(b) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

(c) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,

(d) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline (BIBW2992),

(e) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-(tetrahydropyran-4-yloxy)-quinazoline,

(f) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(g) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-3-yl)methoxy]-quinazoline,

(h) 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(i) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(j) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,

(k) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, and

(r) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-(dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

or a pharmaceutically acceptable salt thereof.

The first aspect of the present invention therefore includes, as a sub-aspect (A), a method of treating cancer comprising pre-selection of cancer patients for EGFR and/or HER2 mutations and administering a therapeutically effective amount of a compound of formula (I) to a pre-selected cancer patient shown to carry an EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or with a tumor harboring an activating HER2 mutation, optionally in combination with radiotherapy, radio-immunotherapy and/or tumour resection by surgery.

Accordingly, the second aspect of the present invention includes, as a sub-aspect (B), the use of a compound of formula (I) for the manufacture of a medicament for the treatment of cancer in a pre-selected cancer patient shown to carry an EGFR mutation in the tyrosine kinase domain of the EGF receptor and/or with a tumor harboring an activating HER2 mutation.

Method of Treatment:

The method of treatment according to the invention comprises administration of a therapeutically effective amount of a compound of formula (I), optionally in form of its tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally in form of the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs or physiologically functional derivatives thereof, to a patient in need thereof, wherein the active ingredient is administered orally, enterically, transdermally, intravenously, peritoneally or by injection, preferably orally. The patient preferably is a human patient.

Dosage:

The compounds of formula (I) may be administered to the human patient in a daily dose of 0.01-4 mg/kg of body weight (bw), preferably 0.1-2 mg/kg, particularly preferred in a dose of 0.2-1.3 mg/kg bw. For oral treatment the compounds of formula (I) may be administered daily in a total dose of 10, 20, 30, 40, 50, 60, 70, 100, 200, or 300 mg, optionally divided into multiple doses, e.g. 1 to 3 doses to be administered through the day. Preferably the oral daily dose is administered only once a time. These doses can be applied with any of the compounds of formula (I), e.g. with BIBW2992 or an equivalent dose of BIBW2992MA$_2$ containing respective amounts of the active base component. Especially for higher doses periods of treatment should alternate with periods of recovery, without administering the active of formula (I). For instance, treatment could follow a "7 day on-7 day off", a "14 day on-14 day off", a "21 day on 7 day off" or a continuous dosing schedule. "On-off" time periods can be chosen shorter, especially if higher doses are administered, or individually adapted to the needs of the patient. The dosage for intravenous use of a compound of formula (I), e.g. of BIBW2992MA$_2$ may be 1-1000 mg, preferably 5-300 mg, particularly preferred 10-100 mg (dosages refer to the base form BIBW2992), either given as a bolus or, especially if higher doses are applied, as a slow intravenous infusion over several hours, e.g. over about 1, 2, 4, 6, 10, 12 or 24 hours.

In one embodiment the invention relates to the method of treatment described above, characterised in that a compound of formula (I), or its polymorph, metabolite, hydrate, solvate, an individual optical isomer, mixtures of the individual enantiomers or racemates thereof, or a pharmaceutically acceptable salt thereof, is administered intermittent or in a daily dosage such that the plasma level of the active substance preferably lies between 10 and 5000 nM for at least 12 hours of the dosing interval.

However, it may optionally be necessary to deviate from the amounts specified, depending on the body weight or method of administration, the individual response to the medication, the nature of the formulation used and the time or interval over which it is administered. Thus, in some cases, it may be sufficient to use less than the minimum quantity specified above, while in other cases the upper limit specified will have to be exceeded. When large amounts are administered it may be advisable to spread them over the day in a number of single doses.

A compound of formula (I), its tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts, solvates, hydrates, polymorphs, physiologically functional derivatives or prodrugs thereof, may be used in monotherapy or combined with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances.

Pharmaceutical Formulations:

Suitable pharmaceutical preparations for the use in accordance with the invention include, for example, tablets, capsules, suppositories, solutions, and particularly solutions for injection (s.c., i.v., i.m.) and infusion, syrups, emulsions or dispersible powders. The amount of pharmaceutically active compound in each case should be in the range from 0.1-90 wt. %, preferably 0.5-50 wt. % of the total composition, i.e. in amounts which are sufficient to achieve the dosage range given below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as the

diluent organic solvents may optionally be used as solubilisers or auxiliary solvents, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Suitable excipients may be, for example, water, pharmaceutically acceptable organic solvents, such as paraffins (e.g. petroleum fractions), oils of vegetable origin (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolin, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silica and silicates), sugar (e.g. glucose, lactose and dextrose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered in the usual way, preferably by oral or transdermal route, particularly preferably by oral route. When administered orally the tablets may, of course, contain additives, such as e.g. sodium citrate, calcium carbonate and dicalcium phosphate together with various additives, such as starch, preferably potato starch, gelatine and the like, in addition to the abovementioned carriers. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to form tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients. For parenteral use, solutions of the active substances may be prepared using suitable liquid carrier materials.

The following Examples serve to illustrate the invention without restricting it:

Example 1

Molecular Potency and Selectivity of BIBW 2992 Compared to Prior Art Compounds

The data summarized in table 1 were obtained using standard in-solution kinase assays performed at saturating ATP concentrations measuring incorporation of phosphate into poly (GluTyr). The same conditions were used for the different compounds in any kinase assay for direct comparison. IC50 values were generated from 12-point dose-response curves run in triplicates.

TABLE 1

BIBW 2992 is a potent and selective dual inhibitor of the EGFR and HER2 kinases

Code	EGFR-Kinase [nM]	HER2 Kinase [nM]	β-InsR Kinase [nM]	VEGFR-2 Kinase [nM]	HGFR Kinase [nM]	c-src Kinase [nM]
gefitinib (ZD-1839)	3	1100	>100000	>100000	>100000	>100000
erlotinib (OSI-774)	2	238	>100000	>100000	>100000	>100000
canertinib (CI-1033)	0.3	30	>100000	24900	>100000	1480
lapatinib (GW-2016)	3	15	>100000	>100000	>20000	>20000
BIBW 2992	0.5	14	>100000	>100000	13000	>4000

Example 2

Inhibition of EGF-Induced EGFR, and Constitutive HER2 Receptor Phosphorylation by BIBW 2992, Compared to Prior Art Compounds

EC50 values were generated from 12-point dose-response curves. For receptor phosphorylation assays cells were pre-incubated for 1 h with test compound. Cells were then either stimulated with EGF (100 ng/ml for 20 min) or directly harvested and tested for pEGFR or pHER2 by ELISA. Propidium iodide based assays were used to assess the proliferation of BT-474 cells in vitro. The compounds were tested under conditions allowing direct direct comparison.

Dual EGFR/HER2 inhibition results in more potent inhibition of cellular proliferation

TABLE 2

Cellular potency of BIBW 2992

	Receptor Phosphorylation				
Compound	A431 EGFR-PO_4 EC_{50} [nM]	NIH3T3 HER2-PO_4 EC_{50} [nM]	N87 HER2-PO_4 EC_{50} [nM]	BT-474 HER2-PO_4 EC_{50} [nM]	Proliferation BT-474 EC_{50} [nM]
gefitinib (ZD-1839)	35	2300	541	3710	1070
erlotinib (OsI-774)	5	734	468	930	829
canertinib (CI-1033)	22	85	288	184	66
lapatinib (GW-2016)	105	171	101	99	52
BIBW 2992	13	71	48	35	12

Example 3

Induction of Apoptosis by BIBW 2992

NCI-N87 gastric cancer cells were treated in vitro with 250 nM BIBW 2992. At indicated time points cells were harvested and samples were analyzed for free nucleosomes (apoptosis hallmark) using the Cell death ELISA kit #1774425 from Roche Diagnostics. Results are shown in FIG. **1** (Appendix).

The following Examples show that once daily dosing of BIBW 2992 significantly inhibits, in a dose dependent manner, the growth of a variety of human tumor xenografts in nude mice:

Example 4

Effect of BIBW 2992 on the Growth of Preexisting HNSCC FaDu Xenografts

Mice carrying established tumors (50-100 mm3) were treated orally, once daily at indicated doses. On the last day of treatment plasma samples were collected and analyzed for compound levels. Results are shown in FIG. **2** (Appendix).

Example 5

Effect of BIBW 2992 on the Growth of MDA-MB-453 and SKOV-3 Xenografts

Mice carrying established tumors (50-100 mm3) were treated orally, once daily at indicated doses with the respective compounds. On the last day of treatment plasma samples were collected and analyzed for compound levels. Results are shown in FIG. **3** (Appendix).

Example 6

Effect of BIBW 2992 on the Growth of Large NCI-N87 Xenografts

Mice carrying established tumors (Panel A: 50-100 mm3; Panel B: 450 mm3) were treated once daily p.o. with BIBW 2992 or once weekly i.v. with Herceptin at indicated doses. Daily oral treatment with BIBW 2992 induces regression of NCI-N87 xenografts. Results are shown in FIG. **4** (Appendix).

Example 7

Pharmacodynamic Evaluation of BIBW 2992 in Several Xenograft Models

Mice carrying established tumors (50-100 mm^3), were treated orally, once daily at indicated doses with the respective compounds. On the last day of treatment plasma samples were collected and analyzed for compound levels.

Daily oral treatment with BIBW 2992 at a dose of 20 mg/kg results in full anti-tumor activity in various xenograft models. Results are summarized in table 3.

TABLE 3

Model	Dose [mg/kg/d]	T/C [%]	Cmax [nM]	AUC [nM*h]
A431	30	2	587	4007
A431	20	2	285	3198

TABLE 3-continued

Model	Dose [mg/kg/d]	T/C [%]	Cmax [nM]	AUC [nM*h]
SKOV-3	20	3	236	2156
MDA-453	20	3	83	972
N87	20	4	80	1075
SKOV-3	15	13	83	589
N87	10	64	66	445
A431	10	80	87	382
A431	3	100	8	21

The T/C (Treated/Control) value corresponds to a % of control value:
median value in the treated group in relation to median value of tumor size in the control group (usually N=10) at the end of the experiment, set to 100% (e.g.: a median value in the treated group of 200 mm^3 in relation to a median value in the control group of 1000 mm^3 results a T/C value of 20%).

Example 8

Response of Patients Treated with BIBW2992

(a) One female patient with metastatic adenocarcinoma of the lung (NSCLC) treated with BIBW2992 MA2 at 10 mg daily (dose refers to the base form; continuous administration schedule) had a confirmed partial response after two months of treatment. The pulmonary lesions have clearly shrunk by >35%, confirmed with a repeat CT scan in 4 weeks. CT scans done in regular intervals confirm the continuation of the partial response. The patient treated developed brain metastases on treatment and increasing the dose of BIBW2992 to 40 mg daily has led to a response in her cerebral disease. This patient remains on treatment 23 months after starting BIBW 2992. This patient's tumour cells have a complex heterozygous EGFR mutation including a deletion and missense mutations of 4-amino acids in the kinase domain, but a wildtype HER2 domain.

(b) Another female patient with non-small cell lung cancer, pleural tumours and mediastinal lymph nodes treated with BIBW2992 MA2 also treated in a continuous dosing schedule at 40 mg daily did develop a partial response as measured by a CT scan after two months of treatment. Five target lesions had been identified; the sum thereof has gone down from 7.3 to 2.6 cm, a decrease of 65%. The patient remains in partial response 14 months after starting treatment with BIBW 2992. An in-frame deletion of 5 amino acids in the same region of the kinase domain has been detected in this patient.

(c) Using a 14 day on 14 day off schedule 2 patients with parotid tumors, one patient with esophageal cancer, one patient with colorectal cancer, one patient with breast cancer, one patient with thyroid cancer and one patient with other endocrine cancer have had stable disease for at least 6 months and have been treated for more than 6 months.

(d) In a continuous dosing schedule and in addition to the above mentioned non-small cell lung cancer patients with partial remissions, a patient with thymic cancer (40 mg daily) and a patient with ovarian cancer (20 mg daily) have had stable disease for at least six months.

(e) In a combined treatment schedule with docetaxel (given every 3 weeks) and BIBW 2992 given for 3 days after the administration of docetaxel one patient had a complete response (breast cancer) and one had partial response (oesophageal).

(f) In a combined treatment schedule with docetaxel (given every 3 weeks) and BIBW 2992 given for 20 or 13 days after the administration of docetaxel, two patients had a partial responses (ovarian and non-small cell lung cancer).

Example 9

Coated Immediate-Release Tablets Containing 75 mg of Active Substance by Dry-Granulation Process

Composition:

1 tablet contains:

active substance	75.0 mg
calcium phosphate anhydrous	108.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.5 mg
hydroxypropylmethylcellulose	7.5 mg
polyethylene glycol	1.0 mg
polydextrose	5.0 mg
talc	1.0 mg
pigments	0.5 mg
water (volatile)	
	245.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Ribbons are produced in a roller-compactor and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

Tablet shape: 9 mm round, bi-convex

The tablet cores are subsequently coated with an aqueous film-coat consisting essentially of hydroxypropylmethylcellulose, polyethylene glycol, polydextrose, talc and pigments.

Weight of coated tablet: 245 mg.

Example 10

Extended-Release Tablets Containing 100 mg of Active Substance by Organic Granulation Granulation Process

1 tablet contains:

active substance	100.0 mg
lactose	34.0 mg
hydroxypropylmethylcellulose	80 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
ethanol (volatile)	
	220.0 mg

Preparation:

The active substance, lactose and hydroxypropylmethylcellulose are mixed together and uniformly moistened with solution of the polyvinylpyrrolidone in ethanol. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50° C. it is screened again (1.5 mm mesh size) and the lubricant is added. The final blend is compressed to form tablets.

Weight of tablet: 220 mg

Tablet shape: 10 mm, flat-faced, with bevelled edges.

Example 11

Tablets Containing 150 mg of Active Substance by Aqueous Granulation Process

1 tablet contains:

active substance	150.0 mg
powdered lactose	98.0 mg
corn starch	40.0 mg
colloidal silica	1.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45° C., are passed through the same screen again and mixed with the specified amount of magnesium stearate and colloidal silica. Tablets are pressed from thefinal blend.

Weight of tablet: 300 mg

Tablet shape: 14 mm×6.8 mm, oblong biconvex with embossement

Example 12

Hard Capsules Containing 150 mg of Active Substance in Granules

Composition:

1 capsule contains:

active substance	150.0 mg
microcrystalline cellulose	80.0 mg
lactose (spray-dried)	87.0 mg
colloidal silica	10.0 mg
	320.0 mg

Preparation:

The active substance is mixed with the excipients in a high-shear mixer, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatin capsules.

Capsule filling: 320 mg

Capsuleshape: size 1, opaque hard capsule.

Example 13

Hard Capsules Containing 150 mg of Active Substance as a Liquid Fill

Composition:

1 capsule contains:

active substance	150.0 mg
groundnut oil	300.0 mg
colloidal silica	10.0 mg
	460.0 mg

Preparation:

The active substance is dissolved in the excipient inside a homogenizer and the colloidal silica is added for adjustment of viscosity. The finished mixture is filled into size 1 hard gelatin capsules.

Capsule filling: 460 mg

Capsuleshape: size 0, opaque hard capsules.

Example 14

Suppositories Containing 150 mg of Active Substance

Composition:

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously suspended therein and the melt is poured into chilled moulds.

Example 15

Suspension Containing 50 mg of Active Substance

Composition:

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water	ad 100.0 ml

Preparation:

The distilled water is heated to 70° C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stilling. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 16

Ampoules Containing 10 mg Active Substance

Composition:

1 ampoule contains:

active substance	10.0 mg
0.01N hydrochloric acid.	q.s
sodium chloride	q.s.
double-distilled water	ad 2.0 ml

Preparation:

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with sodium chloride, filtered sterile and transferred into 2 ml ampoules with subsequent steam sterilization.

Example 17

Ampoules Containing 50 mg of Active Substance

Composition:

1 ampoule contains:

active substance	50.0 mg
0.01N hydrochloric acid	q.s.
sodium chloride	q.s.
double-distilled water	ad 10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with sodium chloride, filtered sterile and transferred into 10 ml ampoules with subsequent steam sterilization.

Example 18

Capsules for Powder Inhalation Containing 5 mg of Active Substance

Composition:

1 capsule contains:

active substance	5.0 mg
lactose for inhalation	15.0 mg
	20.0 mg

Preparation:

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg). weight of capsule: 70.0 mg size of capsule 3

Example 19

Solution for Inhalation for Hand-Held Nebulisers Containing 2.5 mg Active Substance

Composition:

1 spray contains:

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	2.500 mg
ethanol/water (50/50 m/m)	ad 15.000 mg

Preparation:

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered sterile and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

The invention claimed is:

1. A method for treating metastatic non-small cell lung cancer (NSCLC) of squamous histology in a second line patient having failed at least one prior chemotherapy regimen, the method comprising administering to said patient a therapeutically effective amount of the compound 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, or a physiologically acceptable salt thereof.

2. The method of claim **1**, wherein the 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, or a physiologically acceptable salt thereof, is used in monotherapy or in combination with another anti-tumour therapeutic agent.

3. The method of claim **2**, wherein the other anti-tumour therapeutic agent is selected from the group consisting topoisomerase inhibitors, mitosis inhibitors, compounds which interact with nucleic acids, hormone antagonists, inhibitors of metabolic processes, cytokines, and antibodies.

4. The method of claim **2**, wherein the other anti-tumour therapeutic agent is cis-platinum.

5. The method of claim **2**, wherein the compound is 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline dimaleate.

* * * * *

EXHIBIT D

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GILOTRIF safely and effectively. See full prescribing information for GILOTRIF.

GILOTRIF® (afatinib) tablets, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage,	
Previously Treated, Metastatic Squamous NSCLC (1.2)	4/2016
Dosage and Administration, Recommended Dose (2.2)	4/2016
Warnings and Precautions (5)	4/2016

----------INDICATIONS AND USAGE----------

GILOTRIF is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (1.1)
  Limitation of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have other EGFR mutations (1.1)
- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose: 40 mg orally, once daily (2.2)
- Renal impairment: 30 mg orally, once daily in patients with severe renal impairment (2.2, 8.6, 12.3)
- Instruct patients to take GILOTRIF at least 1 hour before or 2 hours after a meal (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 40 mg, 30 mg, and 20 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Diarrhea: Diarrhea may result in dehydration and renal failure. Withhold GILOTRIF for severe and prolonged diarrhea not responsive to anti-diarrheal agents. (2.3, 5.1)
- Bullous and exfoliative skin disorders: Severe bullous, blistering, and exfoliating lesions occurred in 0.2% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)
- Interstitial lung disease (ILD): Occurs in 1.6% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)
- Hepatic toxicity: Fatal hepatic impairment occurs in 0.2% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- Keratitis: Occurs in 0.7% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)
- Embryo-fetal toxicity: Can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%) were diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Co-administration of P-gp inhibitors can increase afatinib exposure. Reduce GILOTRIF by 10 mg per day if not tolerated. Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase GILOTRIF by 10 mg per day as tolerated. (2.3, 7)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 EGFR Mutation-Positive, Metastatic Non-Small Cell Lung Cancer

GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test *[see Clinical Studies (14.1)]*.

Limitation of Use: The safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations *[see Clinical Studies (14.1)]*.

1.2 Previously Treated, Metastatic Squamous NSCLC

GILOTRIF is indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for EGFR Mutation-Positive Metastatic NSCLC

Select patients for first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens *[see Indications and Usage (1.1) and Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dose

The recommended dose of GILOTRIF is 40 mg orally, once daily until disease progression or no longer tolerated by the patient.

Severe Renal Impairment

The recommended dose of GILOTRIF in patients with severe renal impairment (estimated glomerular filtration rate [eGFR*] 15 to 29 mL/min /1.73 m^2) is 30 mg orally, once daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

*Use the Modification of Diet in Renal Disease [MDRD] formula to estimate eGFR.

Take GILOTRIF at least 1 hour before or 2 hours after a meal.

Do not take a missed dose within 12 hours of the next dose.

2.3 Dose Modifications for Adverse Reactions

Withhold GILOTRIF for any adverse reactions of:

- NCI CTCAE* Grade 3 or higher
- Diarrhea of Grade 2 or higher persisting for 2 or more consecutive days while taking anti-diarrheal medication *[see Warnings and Precautions (5.1)]*
- Cutaneous reactions of Grade 2 that are prolonged (lasting more than 7 days) or intolerable *[see Warnings and Precautions (5.2)]*
- Renal impairment of Grade 2 or higher *[see Warnings and Precautions (5.1)]*

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 3.0

Resume treatment when the adverse reaction fully resolves, returns to baseline, or improves to Grade 1. Reinstitute GILOTRIF at a reduced dose, i.e., 10 mg per day less than the dose at which the adverse reaction occurred.

Permanently discontinue GILOTRIF for:

- Life-threatening bullous, blistering, or exfoliative skin lesions *[see Warnings and Precautions (5.2)]*
- Confirmed interstitial lung disease (ILD) *[see Warnings and Precautions (5.3)]*
- Severe drug-induced hepatic impairment *[see Warnings and Precautions (5.4)]*
- Persistent ulcerative keratitis *[see Warnings and Precautions (5.5)]*
- Symptomatic left ventricular dysfunction *[see Adverse Reactions (6.1)]*
- Severe or intolerable adverse reaction occurring at a dose of 20 mg per day

2.4 Dose Modifications for Drug Interactions

P-gp Inhibitors

Reduce GILOTRIF daily dose by 10 mg if not tolerated for patients who require therapy with a P-glycoprotein (P-gp) inhibitor. Resume the previous dose after discontinuation of the P-gp inhibitor as tolerated *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

P-gp Inducers

Increase GILOTRIF daily dose by 10 mg as tolerated for patients who require chronic therapy with a P-gp inducer. Resume the previous dose 2 to 3 days after discontinuation of the P-gp inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

GILOTRIF is available as:

40 mg tablets: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T40” on one side and the Boehringer Ingelheim company symbol on the other side.

30 mg tablets: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with “T30” on one side and the Boehringer Ingelheim company symbol on the other side.

20 mg tablets: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with “T20” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea has resulted in dehydration with or without renal impairment across the clinical experience; some cases were fatal. Grade 3-4 diarrhea occurred in 697 (16%) of the 4257 patients who received GILOTRIF across 44 clinical trials. In Study 1, diarrhea occurred in 96% of patients treated with GILOTRIF (n=229), of which 15% were Grade 3 in severity and occurred within the first 6 weeks. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with GILOTRIF, of which 1.3% were Grade 3. In Study 2, diarrhea occurred in 75% of patients treated with GILOTRIF (n=392), of which 10% were Grade 3 in severity and 0.8% were Grade 4 in severity. Renal impairment as a consequence of diarrhea occurred in 7% of patients treated with GILOTRIF, of which 2% were Grade 3 *[see Adverse Reactions (6.1)]*.

For patients who develop prolonged Grade 2 diarrhea lasting more than 48 hours, or greater than or equal to Grade 3 diarrhea, withhold GILOTRIF until diarrhea resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction *[see Dosage and Administration (2.3)]*. Provide patients with an anti-diarrheal agent (e.g., loperamide) for self-administration at the onset of diarrhea and instruct patients to continue anti-diarrheal therapy until loose bowel movements cease for 12 hours.

5.2 Bullous and Exfoliative Skin Disorders

Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of the 4257 patients who received GILOTRIF across clinical trials. In Study 1, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. In Study 2, the overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 70%, and the incidence of Grade 3 cutaneous reactions was 7%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 1.5% *[see Adverse Reactions (6.1)]*.

Discontinue GILOTRIF in patients who develop life-threatening bullous, blistering, or exfoliating lesions. For patients who develop prolonged Grade 2 cutaneous adverse reactions lasting more than 7 days, intolerable Grade 2, or Grade 3 cutaneous reactions, withhold GILOTRIF until the adverse reaction resolves to Grade 1 or less, and resume GILOTRIF with appropriate dose reduction *[see Dosage and Administration (2.3)]*.

Postmarketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving GILOTRIF. The cases of TEN and SJS bullous skin reactions result from a distinct and separate mechanism of toxicity than the bullous skin lesions secondary to the pharmacologic action of the drug on the epidermal growth factor receptor. Discontinue GILOTRIF if TEN or SJS is suspected *[see Dosage and Administration (2.3)]*.

5.3 Interstitial Lung Disease (ILD)

Interstitial lung disease or ILD-like adverse reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.6% of the 4257 patients who received GILOTRIF across clinical trials; of these, 0.4% were fatal. The incidence of ILD appeared to be higher in Asian patients (2.3%; 38/1657) as compared to Whites (1.0%; 23/2241). In Study 1, the incidence of Grade ≥3 ILD was 1.3% and resulted in death in 1% of GILOTRIF-treated patients. In Study 2, the incidence of Grade ≥3 ILD was 0.9% and resulted in death in 0.8% of GILOTRIF-treated patients.

Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD *[see Dosage and Administration (2.3)]*.

5.4 Hepatic Toxicity

In 4257 patients who received GILOTRIF across clinical trials, 9.7% had liver test abnormalities, of which 0.2% were fatal. In Study 1, liver test abnormalities of any grade occurred in 17.5% of the patients treated with GILOTRIF, of which 3.5% had Grade 3-4 liver test abnormalities. In Study 2, liver test abnormalities of any grade occurred in 6% of the patients treated with GILOTRIF, of which 0.2% had Grade 3-4 liver test abnormalities.

Obtain periodic liver testing in patients during treatment with GILOTRIF. Withhold GILOTRIF in patients who develop worsening of liver function *[see Dosage and Administration (2.3)]*. In patients who develop severe hepatic impairment while taking GILOTRIF, treatment should be discontinued.

5.5 Keratitis

Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with GILOTRIF among 4257 patients across clinical trials, of which 0.05% of patients experienced Grade 3 keratitis. Keratitis was reported in 2.2% patients in Study 1, with Grade 3 in 0.4%. In Study 2, keratitis was reported in 0.3% patients; there were no patients with ≥Grade 3 keratitis.

Withhold GILOTRIF during evaluation of patients with suspected keratitis, and if diagnosis of ulcerative keratitis is confirmed, treatment with GILOTRIF should be interrupted or discontinued *[see Dosage and*

Administration (2.3)]. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GILOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye *[see Adverse Reactions (6.1)]*. Contact lens use is also a risk factor for keratitis and ulceration.

5.6 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1 and 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Diarrhea *[see Warnings and Precautions (5.1)]*
- Bullous and Exfoliative Skin Disorders *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.4)]*
- Keratitis *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to GILOTRIF for clinically significant adverse reactions in 4257 patients enrolled in Studies 1 (n=229) and 2 (n=392), and 3636 patients with cancer enrolled in 42 studies of GILOTRIF administered alone or in combination with other anti-neoplastic drugs at GILOTRIF doses ranging from 10-70 mg daily or at doses 10-160 mg in other regimens. The mean exposure was 5.5 months. The population included patients with various cancers, the most common of which were NSCLC, breast, colorectal, brain, and head and neck.

The data described below reflect exposure to GILOTRIF as a single agent in Study 1, a randomized, active-controlled trial conducted in patients with EGFR mutation-positive, metastatic NSCLC, and in Study 2, a randomized, active-controlled trial in patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

<u>EGFR Mutation-Positive, Metastatic NSCLC</u>

The data in Tables 1 and 2 below reflect the exposure of 229 EGFR-tyrosine kinase inhibitor-naïve, GILOTRIF-treated patients with EGFR mutation-positive, metastatic, non-squamous NSCLC enrolled in a randomized, multicenter, open-label trial (Study 1). Patients received GILOTRIF 40 mg daily until documented disease progression or intolerance to the therapy. A total of 111 patients were treated with pemetrexed/cisplatin. Patients were treated with pemetrexed 500 mg/m² followed after 30 minutes by cisplatin 75 mg/m² every three weeks for a maximum of six treatment courses.

The median exposure was 11 months for patients treated with GILOTRIF and 3.4 months for patients treated with pemetrexed/cisplatin. The overall trial population had a median age of 61 years; 61% of patients in the GILOTRIF arm and 60% of patients in the pemetrexed/cisplatin arm were younger than 65 years. A total of

64% of patients on GILOTRIF and 67% of pemetrexed/cisplatin patients were female. More than two-thirds of patients were from Asia (GILOTRIF 70%; pemetrexed/cisplatin 72%).

Serious adverse reactions were reported in 29% of patients treated with GILOTRIF. The most frequent serious adverse reactions reported in patients treated with GILOTRIF were diarrhea (6.6%); vomiting (4.8%); and dyspnea, fatigue, and hypokalemia (1.7% each). Fatal adverse reactions in GILOTRIF-treated patients in Study 1 included pulmonary toxicity/ILD-like adverse reactions (1.3%), sepsis (0.43%), and pneumonia (0.43%).

Dose reductions due to adverse reactions were required in 57% of GILOTRIF-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (20%), rash/acne (19%), paronychia (14%), and stomatitis (10%).

Discontinuation of therapy in GILOTRIF-treated patients for adverse reactions was 14.0%. The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (1.3%), ILD (0.9%), and paronychia (0.9%).

Clinical trials of GILOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In Study 1, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GILOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GILOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to chemotherapy-treated patients (0.9%; n=1).

Tables 1 and 2 summarize common adverse reactions and laboratory abnormalities in Study 1.

Table 1 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in Study 1*

Adverse Reaction	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grade 3† (%)	All Grades (%)	Grade 3† (%)
Gastrointestinal disorders				
Diarrhea	96	15	23	2
Stomatitis[1]	71	9	15	1
Cheilitis	12	0	1	0
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	90	16	11	0
Pruritus	21	0	1	0
Dry skin	31	0	2	0
Infections				
Paronychia[3]	58	11	0	0
Cystitis	13	1	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	17	0	2	1
Rhinorrhea	11	0	6	0
Investigations				
Weight decreased	17	1	14	1
General disorders and administration site conditions				
Pyrexia	12	0	6	0
Eye disorders				
Conjunctivitis	11	0	3	0

*NCI CTCAE v 3.0

†None of the adverse reactions in this table except stomatitis (one patient on GILOTRIF [0.4%]) were Grade 4 in severity.

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes acne, acne pustular, dermatitis, acneiform dermatitis, dermatosis, drug eruption, erythema, exfoliative rash, folliculitis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

[3]Includes paronychia, nail infection, nail bed infection

Other clinically important adverse reactions observed in patients treated with GILOTRIF but that occurred at a higher incidence in pemetrexed/cisplatin-treated patients and not listed elsewhere in section 6 include: decreased appetite (29% Grade 1-4, 4% Grade 3), nausea (25% Grade 1-4, 4% Grade 3), and vomiting (23% Grade 1-4, 4% Grade 3).

Table 2 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Chemotherapy Arm in Study 1*

Laboratory Abnormality	GILOTRIF n=229		Pemetrexed/Cisplatin n=111	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alanine aminotransferase (ALT)	54	2	27	1
Increased alkaline phosphate	51	3	46	1
Decreased creatinine clearance	49	2	47	1
Increased aspartate aminotransferase (AST)	46	3	22	1
Decreased lymphocytes	38	9	32	14
Decreased potassium	30	8	11	3
Increased bilirubin	16	1	8	0

*NCI CTCAE v 3.0

Previously Treated, Metastatic Squamous NSCLC

The safety of GILOTRIF was evaluated in 392 GILOTRIF-treated patients with metastatic squamous NSCLC enrolled in a randomized, multicenter, open-label trial (Study 2). Patients were required to have received at least four cycles of platinum-based chemotherapy, ECOG Performance Status (PS) 0 or 1, and normal left ventricular ejection fraction (LVEF). Patients received GILOTRIF 40 mg once daily (n=392) or erlotinib 150 mg once daily (n=395). Treatment continued until documented disease progression or intolerance to the therapy.

Among the 392 GILOTRIF-treated patients, the median age was 65 years, 53% were 65 years of age or older, 84% were male, 72% were White, 25% were Asian, ECOG PS 0 (32%) or 1 (68%). The median exposure was 2.1 months for patients treated with GILOTRIF, 15% were exposed for at least 6 months, and 5% were exposed for at least 12 months.

Serious adverse reactions occurred in 44% of patients treated with GILOTRIF. The most frequent serious adverse reactions in patients treated with GILOTRIF were pneumonia (6.6%), diarrhea (4.6%), and dehydration and dyspnea (3.1% each). Fatal adverse reactions in GILOTRIF-treated patients included ILD (0.5%), pneumonia (0.3%), respiratory failure (0.3%), acute renal failure (0.3%), and general physical health deterioration (0.3%).

Dose reductions due to adverse reactions were required in 27% of GILOTRIF-treated patients and discontinuation of GILOTRIF for adverse reactions was required for 20%. The most frequent adverse reactions that led to dose reduction in the patients treated with GILOTRIF were diarrhea (15%), rash/acne (5.9%), and stomatitis (3.1%). The most frequent adverse reactions that led to discontinuation in GILOTRIF-treated patients were diarrhea (4.1%) and rash/acne (2.6%). Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in Study 2.

Table 3 Adverse Reactions Reported in ≥10% of GILOTRIF-Treated Patients in Study 2*

Adverse Reaction	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	75	11	41	3
Stomatitis[1]	30	4	11	1
Nausea	21	2	16	1
Vomiting	13	1	10	1
Skin and subcutaneous tissue disorders				
Rash/acneiform dermatitis[2]	70	7	70	11
Pruritus	10	0	13	0
Infections				
Paronychia[3]	11	1	5	0
Metabolism and nutrition disorders				
Decreased appetite	25	3	26	2

*NCI CTCAE v 3.0

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes acne, dermatitis, acneiform dermatitis, eczema, erythema, exfoliative rash, folliculitis, rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin fissures, skin lesion, skin reaction, skin toxicity, skin ulcer

[3]Includes paronychia, nail infection, nail bed infection

Table 4 Laboratory Abnormalities Occurring in ≥10% of GILOTRIF Arm and at ≥2% Higher Incidence than in Erlotinib Arm in Study 2*

Laboratory Abnormality	GILOTRIF n=392		Erlotinib n=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

*NCI CTCAE v 3.0

Other clinically important laboratory abnormalities observed in patients treated with GILOTRIF that are not listed in Table 4 are: increased alanine aminotransferase (10% Grade 1-4; 1% Grade 3-4), increased aspartate aminotransferase (7% Grade 1-4; 1% Grade 3-4), and increased bilirubin (3% Grade 1-4; 0 Grade 3-4).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GILOTRIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Pancreatitis
- Toxic epidermal necrolysis/Stevens Johnson syndrome

7 DRUG INTERACTIONS

Effect of P-glycoprotein (P-gp) Inhibitors and Inducers

Concomitant taking of P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) with GILOTRIF can increase exposure to afatinib *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Concomitant taking of P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital, and St. John's wort) with GILOTRIF can decrease exposure to afatinib *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, GILOTRIF can cause fetal harm when administered to a pregnant woman. There are no available data on the use of GILOTRIF in pregnant women. Administration of afatinib to pregnant rabbits during organogenesis at exposures approximately 0.2 times the exposure in humans at the recommended dose of 40 mg daily resulted in embryotoxicity and, in rabbits showing maternal toxicity, increased abortions at late gestational stages *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rabbits, administration of afatinib to pregnant animals at doses of 5 mg/kg (approximately 0.2 times the exposure by AUC at the recommended human dose of 40 mg daily) or greater during the period of organogenesis caused increased post-implantation loss, and in animals showing maternal toxicity, abortion at late gestational stages. In the same study, at the high dose level of 10 mg/kg (approximately 0.7 times the exposure by AUC at the recommended human dose of 40 mg daily), there were reduced fetal weights, and increases in the incidence of runts, as well as visceral and dermal variations. In an embryo-fetal development study in rats, there were skeletal alterations consisting of incomplete or delayed ossifications and reduced fetal weight at a dose of 16 mg/kg (approximately twice the exposure based on AUC at the recommended human dose of 40 mg daily).

8.2 Lactation

Risk Summary

There are no data on the presence of afatinib in human milk or its effects on the breastfed infant or on milk production. Afatinib was present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from GILOTRIF, advise a lactating woman not to breastfeed during treatment with GILOTRIF and for 2 weeks after the final dose.

Data

Afatinib was present in the milk of lactating rats at concentrations 80 and 150 times higher than those found in plasma at 1 and 6 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

GILOTRIF can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF, and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

Infertility

Based on results from an animal fertility study, GILOTRIF may reduce fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of GILOTRIF in pediatric patients have not been established.

8.5 Geriatric Use

Study 1 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In Study 2, 53% of the 398 patients randomized to receive afatinib were 65 years of age or older and 11% were 75 years or older. In an exploratory subgroup analysis of Study 2, the hazard ratio for overall survival in patients less than 65 years old was 0.68 (95% CI: 0.55, 0.85) and in patients 65 years or older was 0.95 (95% CI: 0.76, 1.19). No overall differences in safety were observed between patients 65 years and older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment have a higher exposure to afatinib than patients with normal renal function. Administer GILOTRIF at a starting dose of 30 mg once daily in patients with severe renal impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild or moderate renal impairment. Dosing recommendations for patients with eGFR <15 mL/min/1.73 m^2 or on dialysis cannot be provided as GILOTRIF has not been studied in these patient populations *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

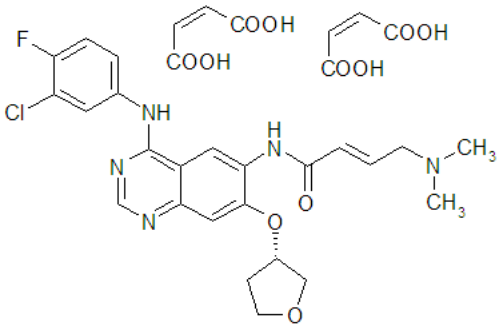
GILOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. Adjustments to the starting dose of GILOTRIF are not necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Closely monitor patients with severe hepatic impairment and adjust GILOTRIF dose if not tolerated *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdose was reported in 2 healthy adolescents each of whom ingested 360 mg of GILOTRIF (as part of a mixed-drug ingestion) resulting in nausea, vomiting, asthenia, dizziness, headache, abdominal pain, and elevated amylase [<1.5 times upper limit of normal (ULN)]. Both subjects recovered.

11 DESCRIPTION

GILOTRIF tablets contain afatinib, a tyrosine kinase inhibitor which is a 4-anilinoquinazoline. Afatinib is presented as the dimaleate salt, with the chemical name 2-butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2*E*)-, (2*Z*)-2-butenedioate (1:2). Its structural formula is:



Afatinib dimaleate is a white to brownish yellow powder, water soluble and hygroscopic, with an empirical formula of $C_{32}H_{33}ClFN_5O_{11}$, and a molecular weight of 718.1 g/mol.

GILOTRIF tablets for oral administration are available in 40 mg, 30 mg, or 20 mg of afatinib (equivalent to 59.12 mg, 44.34 mg, or 29.56 mg afatinib dimaleate, respectively). The inactive ingredients of GILOTRIF are the following: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate and Coating: hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Afatinib covalently binds to the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downregulation of ErbB signaling.

Afatinib demonstrated inhibition of autophosphorylation and *in vitro* proliferation of cell lines expressing wild-type EGFR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations, including some with a secondary T790M mutation, at afatinib concentrations achieved, at least transiently, in patients. In addition, afatinib inhibited *in vitro* proliferation of cell lines overexpressing HER2.

Treatment with afatinib resulted in inhibition of tumor growth in nude mice implanted with tumors either overexpressing wild type EGFR or HER2 or in an EGFR L858R/T790M double mutant model.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of GILOTRIF (50 mg once daily) on the QTc interval was evaluated in an open-label, single-arm study in patients with relapsed or refractory solid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

12.3 Pharmacokinetics

Absorption and Distribution

Following oral administration of GILOTRIF tablets, time to peak afatinib plasma concentrations (T_{max}) is 2 to 5 hours. Maximum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased slightly more than dose proportional in the range of 20 to 50 mg. The geometric mean relative bioavailability of 20 mg GILOTRIF tablets was 92% as compared to an oral solution. *In vitro* binding of afatinib to human plasma proteins is approximately 95%.

A high-fat meal decreased C_{max} by 50% and $AUC_{0-\infty}$ by 39% relative to the fasted condition *[see Dosage and Administration (2.2)]*.

Metabolism and Elimination

Covalent adducts to proteins are the major circulating metabolites of afatinib and enzymatic metabolism of afatinib is minimal.

In humans, excretion of afatinib is primarily *via* the feces (85%) with 4% recovered in the urine following a single oral dose of [^{14}C]-labeled afatinib solution. The parent compound accounted for 88% of the recovered dose.

The elimination half-life of afatinib is 37 hours after repeat dosing in cancer patients. Steady-state plasma concentrations are achieved within 8 days of repeat dosing of GILOTRIF resulting in an accumulation of 2.8-fold for AUC and 2.1-fold for C_{max}.

Specific Populations

Renal Impairment: A pharmacokinetic study was conducted in 14 subjects with normal (eGFR ≥90 mL/min/1.73 m^2) renal function, 8 subjects with moderate (eGFR=30 to 59 mL/min/1.73 m^2) and 8 subjects with severe (eGFR=15 to 29 mL/min /1.73 m^2) renal impairment. All subjects received a single 40 mg oral dose of GILOTRIF. The geometric mean AUC_{inf} for afatinib was 50% higher in subjects with severe renal impairment and was 22% higher in subjects with moderate renal impairment as compared to subjects with normal renal function. Geometric mean C_{max} was 22% higher in subjects with severe renal impairment and was comparable in subjects with moderate renal impairment as compared to subjects with normal renal function *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*. GILOTRIF has not been studied in patients with eGFR <15 mL/min/1.73 m^2 or on dialysis.

Hepatic Impairment: Afatinib is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on the afatinib exposure following a single dose of

GILOTRIF. Subjects with severe (Child Pugh C) hepatic dysfunction have not been studied *[see Use in Specific Populations (8.7)]*.

Body Weight, Gender, Age, and Race: Based on the population pharmacokinetic analysis, weight, gender, age, and race do not have a clinically important effect on exposure of afatinib.

Drug Interactions

Effect of P-gp Inhibitors and Inducers on Afatinib: The effect of ritonavir dosing time relative to a single oral dose of GILOTRIF was evaluated in healthy subjects taking 40 mg of GILOTRIF alone as compared to those after ritonavir (200 mg twice daily for 3 days) co-administration at 6 hours after GILOTRIF administration. The relative bioavailability for $AUC_{0-\infty}$ and C_{max} of afatinib was 119% and 104% when co-administered with ritonavir, and 111% and 105% when ritonavir was administered 6 hours after taking GILOTRIF. In another study, when ritonavir (200 mg twice daily for 3 days) was administered 1 hour before a 20 mg single dose of GILOTRIF, exposure to afatinib increased by 48% for $AUC_{0-\infty}$ and 39% for C_{max} *[see Drug Interactions (7)]*.

Pre-treatment with a potent inducer of P-gp, rifampicin (600 mg once daily for 7 days) decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) *[see Drug Interactions (7)]*.

P-glycoprotein (P-gp): Based on *in vitro* data, afatinib is a substrate and an inhibitor of P-gp.

Breast Cancer Resistance Protein (BCRP): Based on *in vitro* data, afatinib is a substrate and an inhibitor of the transporter BCRP.

Effect of CYP450 Enzyme Inducers and Inhibitors on Afatinib: *In vitro* data indicated that drug-drug interactions with GILOTRIF due to inhibition or induction of CYP450 enzymes by concomitant medications are unlikely. The metabolites formed by CYP450-dependent reactions were approximately 9% of the total metabolic turnover in sandwich-cultured human hepatocytes. In humans, enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3; the CYP3A4-dependent N-demethylation was not detected.

Effect of Afatinib on CYP450 Enzymes: Afatinib is not an inhibitor or an inducer of CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4) in cultured primary human hepatocytes. Therefore, afatinib is unlikely to affect the metabolism of other drugs that are substrates of CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with afatinib.

A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. No mutagenic or genotoxic potential was identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as in the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay, and an *in vivo* 4-week oral mutation study in the Muta™ Mouse.

In a dedicated fertility study, male and female rats received afatinib daily by oral administration at doses of 4, 6, or 8 mg/kg. In males at doses of 6 mg/kg (approximately equal to the exposure by AUC in patients at the recommended human dose of 40 mg daily) or greater, there was an increase in the incidence of low or no sperm count, though overall fertility was not affected; decreases in sperm count were supported by findings of increased apoptosis in the testes and atrophy in the seminal vesicles and the prostate in general toxicology studies. In females at the high dose of 8 mg/kg (approximately 0.63 times the exposure by AUC in patients at the recommended human dose of 40 mg daily), there was a mild decrease in the number of corpora lutea along with a mild increase in post-implantation loss due to early resorptions. In a 4-week general toxicology study,

female rats had decreases in ovarian weights at all dose levels; organ weight had not fully recovered by the end of a 2-week recovery period.

14 CLINICAL STUDIES

14.1 EGFR Mutation-Positive Non-Small Cell Lung Cancer

The efficacy and safety of GILOTRIF in the first-line treatment of 345 patients with EGFR mutation-positive, metastatic [Stage IV and Stage IIIb with pleural and/or pericardial effusion as classified by the American Joint Commission on Cancer (AJCC, 6th edition)] non-small cell lung cancer (NSCLC) were established in a randomized, multicenter, open-label trial (Study 1). Patients were randomized (2:1) to receive GILOTRIF 40 mg orally once daily (n=230) or up to 6 cycles of pemetrexed/cisplatin (n=115). Randomization was stratified according to EGFR mutation status (exon 19 deletion vs exon 21 L858R vs other) and race (Asian vs non-Asian). The major efficacy outcome was progression-free survival (PFS) as assessed by an independent review committee (IRC). Other efficacy outcomes included overall response rate (ORR) and overall survival (OS). EGFR mutation status was prospectively determined for screening and enrollment of patients by a clinical trial assay (CTA). Tumor samples from 264 patients (178 randomized to GILOTRIF and 86 patients randomized to chemotherapy) were tested retrospectively by the companion diagnostic *therascreen*® EGFR RGQ PCR Kit, which is FDA-approved for selection of patients for GILOTRIF treatment.

Among the patients randomized, 65% were female, median age was 61 years, baseline ECOG performance status was 0 (39%) or 1 (61%), 26% were Caucasian and 72% were Asian. The majority of the patients had a tumor sample with an EGFR mutation categorized by the CTA as either exon 19 deletion (49%) or exon 21 L858R substitution (40%), while the remaining 11% had other mutations.

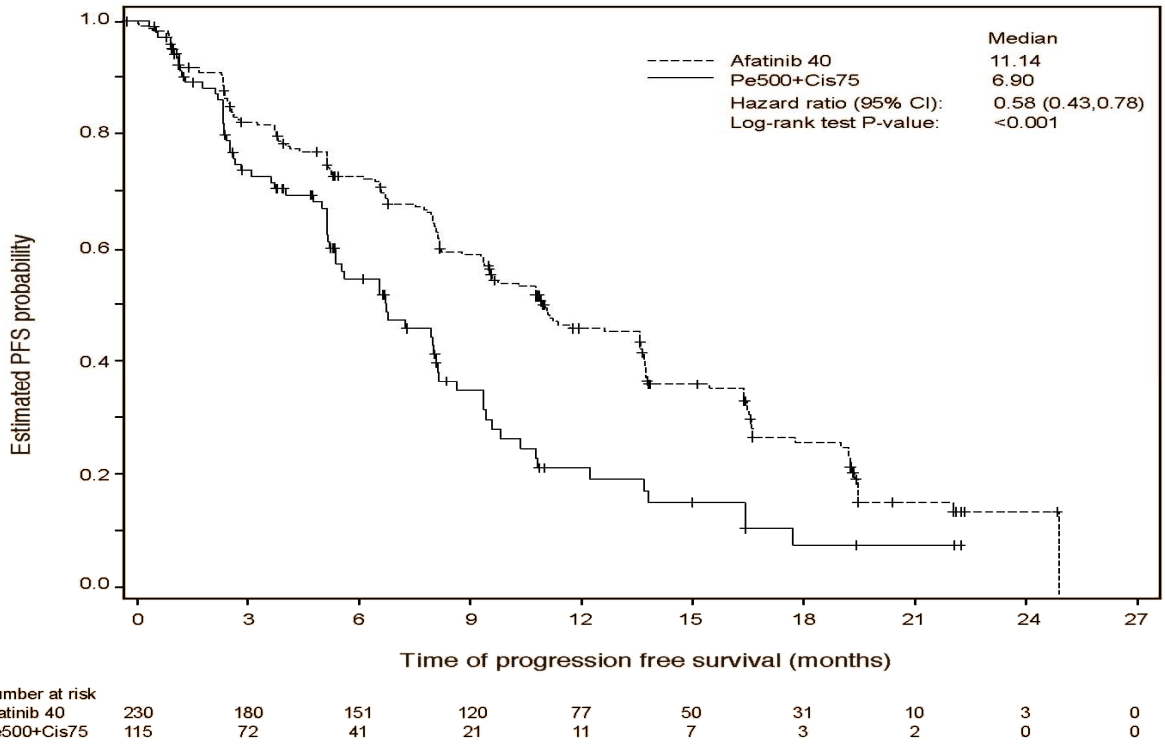
A statistically significant improvement in PFS as determined by the IRC was demonstrated for patients randomized to GILOTRIF compared with those randomized to chemotherapy. See Table 5 and Figure 1. There was no statistically significant difference for overall survival between the treatment arms at the final pre-planned analysis.

Table 5 Efficacy Results

	GILOTRIF (N=230)	**Pemetrexed/Cisplatin (N=115)**
Progression-Free Survival by IRC		
Number of Deaths or Progressions, N (%)	152 (66.1%)	69 (60.0%)
Median Progression-Free Survival (months)	11.1	6.9
95% CI	(9.6, 13.6)	(5.4, 8.2)
HR (95% CI)	0.58 (0.43, 0.78)	
Stratified Log-Rank Test p-value*	<0.001	
Overall Survival		
Number of Deaths, N (%)	140 (60.9%)	73 (63.5%)
Median Overall Survival (months)	28.2	28.2
95% CI	(24.6, 33.6)	(20.7, 33.2)
HR (95% CI)	0.88 (0.66, 1.17)	
Stratified Log-Rank Test p-value*	0.39	
Overall Response Rate (CR + PR) by IRC		
N (%)	116 (50.4%)	22 (19.1%)
Response Duration		
Median (months)	12.5	6.7

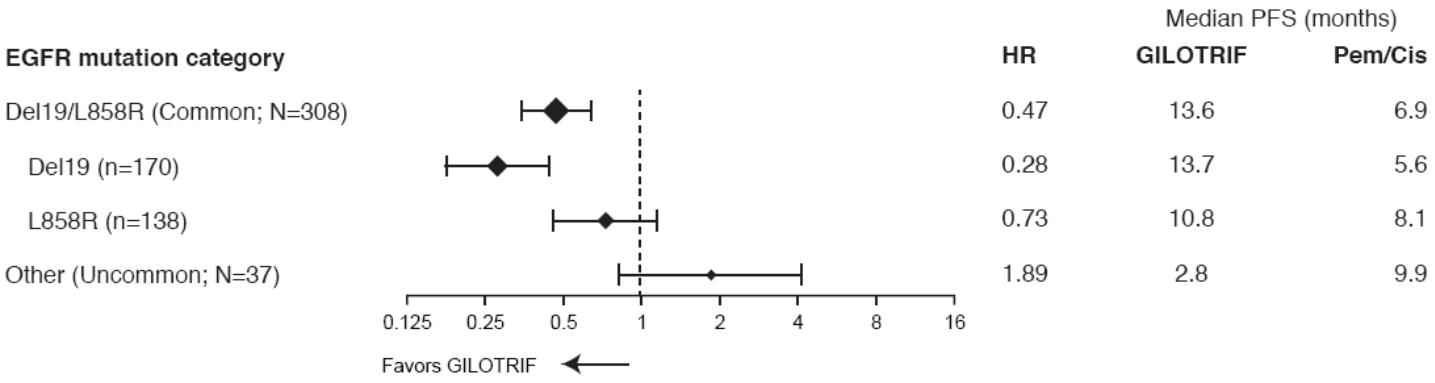
*Stratified by EGFR mutation status and race.
HR=hazard ratio; CR=complete response; PR=partial response

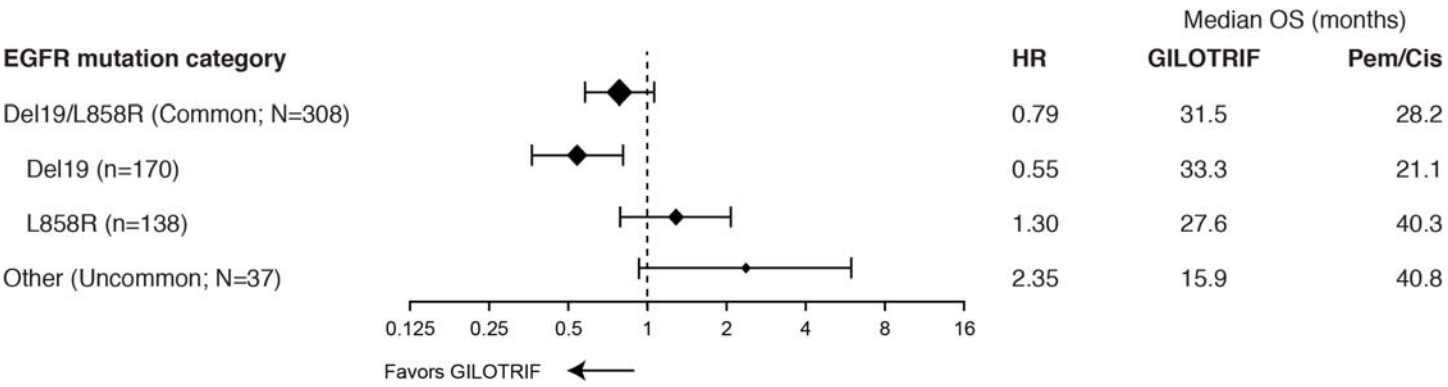
Figure 1 Kaplan-Meier Curve for PFS by Independent Review by Treatment Group



Subgroup analyses were conducted based on the stratification factor of EGFR mutation status (Del19, L858R, other) and mutation category (common [Del19, L858R] vs uncommon [other]). See Figure 2.

Figure 2 Forest Plot of PFS and OS for Common (Del19, L858R) and Uncommon (other) EGFR Mutation Categories





There were 26 GILOTRIF-treated patients in the "other" (uncommon) EGFR mutations subgroup with nine unique mutation patterns. None of these 26 patients achieved a complete response, while four achieved a partial response (see Table 6 below). No responses were seen in GILOTRIF-treated patients with the following mutations: T790M alone (n=2), deletion 19 and T790M (n=3), G719X and T790M (n=1), exon 20 insertion (n=6), and L861Q alone (n=3). There were 11 chemotherapy-treated patients in the "other" uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

Table 6 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the "Other" (Uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

14.2 Previously Treated, Metastatic Squamous NSCLC

The efficacy and safety of GILOTRIF were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). Patients were required to have histologically documented, metastatic squamous NSCLC and have experienced disease progression following an adequate course (≥ 4 cycles) of a platinum-based doublet chemotherapy regimen. Patients were randomized (1:1) to receive GILOTRIF 40 mg or erlotinib 150 mg orally once daily until progression. Randomization was stratified by region (Eastern Asia vs other). The major efficacy outcome measure was PFS as assessed by an independent review committee (IRC) using RECIST v 1.1. Additonal efficacy outcome measures were OS and ORR as assessed by IRC.

Baseline patient demographics of the 795 patients were: median age 64 years (range: 35 to 88); 73% White; 24% Asian; 84% male; 33% ECOG performance status (PS) 0 and 67% ECOG PS 1; and 95% current or former smokers. With regard to tumor characteristics, 96% had squamous cell histology and 3.5% had mixed cell histology. All patients received platinum-based doublet therapy.

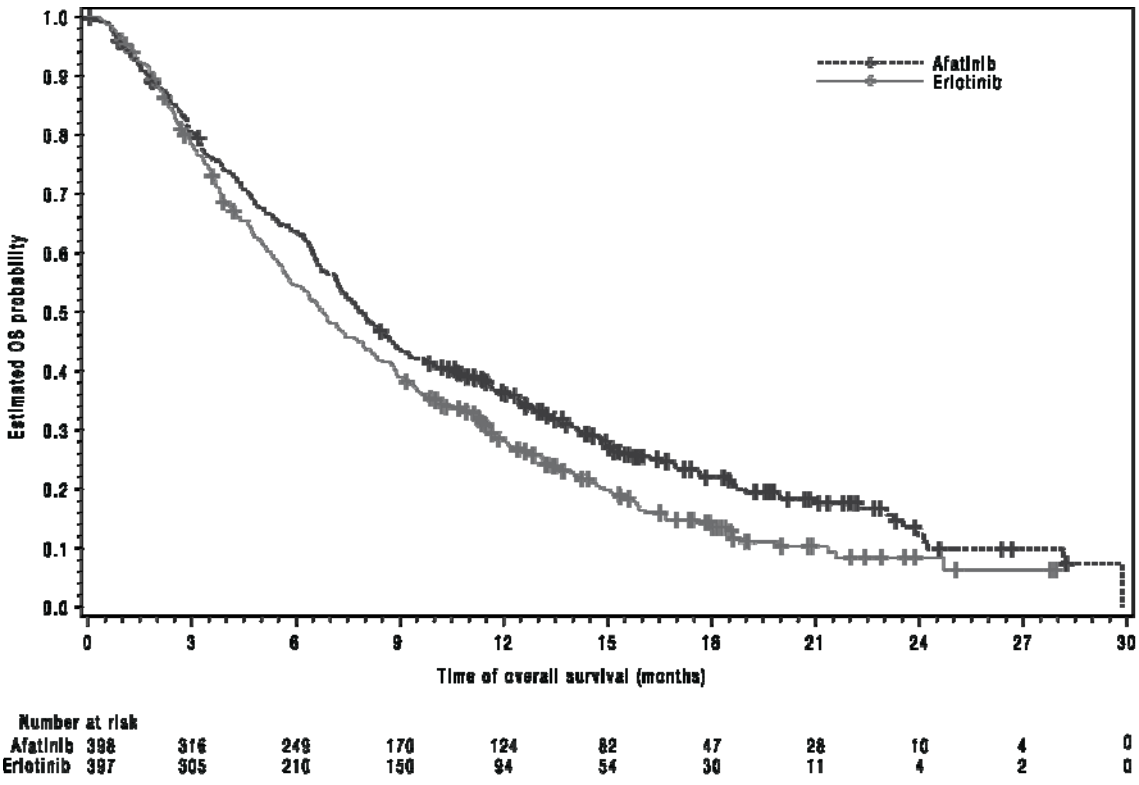
The study demonstrated a statistically significant improvement in PFS and OS for patients randomized to GILOTRIF as compared with erlotinib (see Table 7 and Figure 3).

Table 7 Efficacy Results

	GILOTRIF	Erlotinib
Overall Survival		
	N=398	N=397
Number of Deaths, N (%)	307 (77%)	325 (82%)
Median overall survival (months)	7.9	6.8
95% CI	(7.2, 8.7)	(5.9, 7.8)
HR (95% CI)	0.81 (0.69, 0.95)	
p-value*	0.008	
Progression-Free Survival (PFS) by IRC		
	N=335	N=334
Number of Events, N (%)	202 (60%)	212 (64%)
Median PFS (months)	2.4	1.9
95% CI	(1.9, 2.9)	(1.9, 2.2)
HR (95% CI)	0.82 (0.68, 0.998)	
p-value*	0.0427	
Overall Response Rate (ORR) by IRC		
	N=335	N=334
ORR	3%	2%
(95% CI)	(1.7, 5.8)	(0.8, 4.3)

*Log-rank test stratified by region.
HR=hazard ratio

Figure 3 Kaplan-Meier Curves of Overall Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

GILOTRIF tablets are available as follows:

40 mg: light blue, film-coated, round, biconvex, bevel-edged tablets debossed with "T40" on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0138-30

30 mg: dark blue, film-coated, round, biconvex, bevel-edged tablets debossed with "T30" on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0137-30

20 mg: white to slightly yellowish, film-coated, round, biconvex, bevel-edged tablets debossed with "T20" on one side and the Boehringer Ingelheim company symbol on the other side.
Unit of use bottles of 30 NDC: 0597-0141-30

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Dispense medication in the original container to protect from exposure to high humidity and light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Diarrhea
Advise patients that diarrhea occurs in nearly all patients who receive GILOTRIF. Inform patients that diarrhea may result in dehydration and renal impairment if not treated. Advise patients to notify their physician if diarrhea develops and to seek medical attention promptly for severe or persistent diarrhea *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Bullous and Exfoliative Skin Disorders
Advise patients to minimize sun exposure with protective clothing and use of sunscreen while taking GILOTRIF *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease
Advise patients to immediately report any new or worsening lung symptoms, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, fever *[see Warnings and Precautions (5.3)]*.

Hepatic Toxicity
Advise patients that they will need to undergo liver function monitoring periodically. Advise patients to immediately report any symptoms of a liver problem [e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleeds or bruises more easily than normal, lethargy] *[see Warnings and Precautions (5.4)]*.

Keratitis
Advise patients to immediately report eye problems (e.g., eye pain, swelling, redness, blurred vision, or other vision changes) *[see Warnings and Precautions (5.5)]*.

Left Ventricular Dysfunction
Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath or exercise intolerance, cough, fatigue, swelling of the ankles/legs, palpitations, or sudden weight gain *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

Instructions for Taking GILOTRIF
Advise patients to take GILOTRIF on an empty stomach at least 1 hour before or 2 hours after eating *[see Dosage and Administration (2.2)]*. Advise patients not to take a missed dose within 12 hours of the next dose.

Embryo-Fetal Toxicity
Advise pregnant women and females of reproductive potential that GILOTRIF can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with GILOTRIF and for at least 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise women not to breastfeed during treatment with GILOTRIF and for 2 weeks after the last dose of GILOTRIF *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females and males of reproductive potential of the potential for reduced fertility from GILOTRIF *[see Use in Specific Populations (8.3)]*.

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Ridgefield, CT 06877 USA

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IT5562PJ042016

Patient Information
GILOTRIF® (JEE-loh-trif)
(afatinib) tablets

What is GILOTRIF?

GILOTRIF is a prescription medicine used to treat non-small cell lung cancer (NSCLC):

- that has certain types of abnormal epidermal growth factor receptor (EGFR) genes. Your doctor will perform a test to check for certain types of abnormal EGFR genes, and make sure that GILOTRIF is right for you. GILOTRIF may be used when you have not had previous treatment for cancer that has spread to other parts of your body. It is not known if GILOTRIF is safe and effective in treating lung cancer with other abnormal EGFR genes.

or

- that is squamous type and has spread to other parts of the body after you have tried chemotherapy that contains platinum.

It is not known if GILOTRIF is safe and effective in children.

Before you take GILOTRIF, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver problems
- have lung or breathing problems other than lung cancer
- have a history of severe dry eye or any other eye problems. Tell your doctor if you wear contact lenses.
- have heart problems
- are pregnant or plan to become pregnant. GILOTRIF can harm your unborn baby. You should not become pregnant while taking GILOTRIF.
  - Women who are able to become pregnant should use effective birth control during treatment with GILOTRIF and for at least 2 weeks after your last dose of GILOTRIF. Talk to your doctor about birth control methods that may be right for you.
  - Tell your doctor right away if you become pregnant or think you are pregnant while taking GILOTRIF.
- are breastfeeding or plan to breastfeed. It is not known if GILOTRIF passes into your breast milk. Do not breastfeed while taking GILOTRIF and for 2 weeks after your last dose of GILOTRIF. Talk to your doctor about the best way to feed your baby if you take GILOTRIF.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. GILOTRIF may affect the way other medicines work, and other medicines may affect the way GILOTRIF works.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take GILOTRIF?

- Take GILOTRIF exactly as your doctor tells you to take it.
- Your doctor will tell you how many GILOTRIF tablets to take and when to take them. Do not change your dose or stop GILOTRIF unless your doctor tells you to.
- Take GILOTRIF on an empty stomach at least 1 hour before a meal or 2 hours after a meal.
- If you miss a dose of GILOTRIF, take it as soon as you remember. If it is within 12 hours of your next dose, skip the dose and just take your next dose at your regular time. Do not take 2 doses of GILOTRIF at the same time.
- If you take too much GILOTRIF, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking GILOTRIF?

Limit your time in the sun. GILOTRIF can make your skin sensitive to the sun. You could get or have worsening rash or acne. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin while you are taking GILOTRIF if you have to be in sunlight.

What are the possible side effects of GILOTRIF?

GILOTRIF may cause serious side effects, including:

- **diarrhea.** Diarrhea is common with GILOTRIF and may sometimes be severe. Severe diarrhea can cause loss of too much body fluid (dehydration) and kidney problems that can sometimes lead to death. During your treatment with GILOTRIF, your doctor should prescribe medicines to treat diarrhea. Take this medicine exactly as your doctor tells you to. Tell your doctor if you have diarrhea. Get medical attention right away if your diarrhea does not go away or becomes severe.
- **skin reactions.** GILOTRIF can cause redness, rash, and acne. It is important to get treatment for skin reactions as soon as you notice them. Take medicines to help skin reactions exactly as your doctor tells you to. Get medical attention right away if you develop severe skin reactions such as peeling or blistering of the skin, or blisters in your mouth.

- **lung or breathing problems.** GILOTRIF may cause inflammation of the lung that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening lung problems, or any combination of the following symptoms: trouble breathing or shortness of breath, cough, or fever.
- **liver problems.** GILOTRIF can cause liver problems that can sometimes lead to death. Tell your doctor right away if you have any symptoms of a liver problem which may include:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark or brown (tea colored) urine
  - pain on the upper right side of your stomach area (abdomen)
  - bleeding or bruising more easily than normal
  - feeling very tired

  Your doctor will do blood tests to check your liver function during your treatment with GILOTRIF.
- **eye problems.** Tell your doctor right away if you have symptoms of eye problems which may include:
  - eye pain, swelling, redness, or tearing
  - blurred vision
  - sensitivity to light
  - other changes in your vision
- **heart problems.** Tell your doctor right away if you have symptoms of a heart problem which may include:
  - new or worsening shortness of breath while at rest or with activity
  - cough
  - tiredness
  - swelling of your ankles, feet, or legs
  - feeling that your heart is pounding or racing (palpitations)
  - sudden weight gain

The most common side effects of GILOTRIF include:

- diarrhea
- rash
- mouth sores
- nail inflammation
- dry skin
- acne
- decreased appetite
- nausea
- vomiting
- itching

GILOTRIF may cause decreased fertility in females and males. Talk to your doctor if you have concerns about fertility.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GILOTRIF. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GILOTRIF?

- Store GILOTRIF at room temperature 68°F to 77°F (20°C to 25°C).
- Keep GILOTRIF in the original container and keep the container tightly closed.
- Keep GILOTRIF away from moisture and light.
- Safely throw away (discard) any GILOTRIF that is out of date or no longer needed.

Keep GILOTRIF and all medicines out of the reach of children.

General information about GILOTRIF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use GILOTRIF for a condition for which it was not prescribed. Do not give GILOTRIF to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about GILOTRIF that is written for health professionals.

What are the ingredients in GILOTRIF?

Active ingredient: afatinib

Inactive ingredients: Tablet Core: lactose monohydrate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate. **Tablet Coating:** hypromellose, polyethylene glycol, titanium dioxide, talc, polysorbate 80, FD&C Blue No. 2 (40 mg and 30 mg tablets only).

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For more information, go to www.gilotrif.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906, or scan the code to go to www.gilotrif.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: October 2016